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Cigarette Smoke and the Physiologic Drainage of the Bronchial Tree*

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Cigarette smoke is unique in several ways in comparison with other air pollutants. Most inhaled particulate matter (including bacteria) is removed in the nose, which is highly efficient in its function of cleansing the inspired air and conditioning it for acceptance into the lungs. Foreign matter is deposited mostly in the front third of the nose, so that by the time the air reaches the back part of the nose, it is already almost entirely free of particulate matter, it is saturated with moisture and has a temperature almost up to that of the body.[4,9] By an escalator-like action, the deposited material is carried backward in the mucous blanket from the nose down to the throat, where it is swallowed into the stomach. The relatively small amount of foreign particulate matter which gets through the nose is deposited more or less diffusely in the tracheobronchial tree. The largest particles are deposited first and the medium sized ones go deeper and some of the smallest may reach the alveoli or may even not be deposited at all. Gases are presumably diffusely dissolved and absorbed according to their various solubility patterns.

The case of cigarette smoke is different from other air pollutants. By means of an ingenious, neat little cylindrical device (one might call it actually a miniature furnace), the smoker charges the inspired air with tar droplets and a whole series of gases in concentrations far exceeding that of the densest smog. He first takes the smoke into his mouth in a concentrated form and then, in the pharynx, proceeds to feed it into the next inspiration of cleansed air flowing from the nose, just as this air is ready to enter the larynx and trachea. He by-passes the nose, the natural cleansing mechanism, entirely. Like other particulate matter, as the inspired air flows down, the tar droplets are deposited throughout the whole tracheobronchial tree—even in the alveoli. About half is deposited in ordinary smoking. The deposits are somewhat greater in the proximal portion, where the largest particles settle.[5] In models that have been constructed and studied, it has been found that the deposit is not en-

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tirely even but it tends to be greater just under the vocal cords and in the root of the lung, where the large bronchi begin.[3] How closely this resembles the pattern in living man is not known.

To understand then what happens to foreign particulate matter, once it gains access to the respiratory tract, the physiology of ciliary streaming will be reviewed briefly.

In general, the whole respiratory tract, upper and lower, down to the respiratory bronchioles, is lined by an epithelium covered with cilia. All of these cilia beat with a purposeful stroke that is something like the arm stroke of a swimmer. They beat about 1000 cycles per minute. Each stroke has a 1:3 rhythm, the effective phase being three times as fast as the recovery phase.[1] They are beautifully coordinated and beat in a definite direction—in the nose down and back toward the throat, in the tracheobronchial tree upward toward the larynx and pharynx. Also throughout the whole tract, upper and lower, these cilia are overlaid by an intact blanket or lining of mucus, that is completely changed many times each day. This system is something like an escalator or belt conveyor, the cilia supplying the motive power and the mucous blanket being the conveyor. This moving blanket of mucus is referred to as the ciliary stream.

In the lower tract, the ciliary stream may be likened to a river that begins in tiny branches (the respiratory bronchioles) that join together into ever larger branches until the trachea is reached. If the trachea is split open and laid out flat, it is found to be 5 cm. across. This constitutes the width of the streambed, at that level, of the river that we are describing. The two main bronchi together are about the same size in cross sectional area as the trachea,* but, if they are split open and measured, it will be found that they measure together about 7.5 cm. across. This is the width of the streambed of our river in the main bronchi. With each subsequent branching, as we proceed down the respiratory tract, the combined circumferences become greater; thus the combined width of the streambed in which the river flows becomes greater. In the tiny bronchi, where the ciliary stream originates, the total circumference is many meters in extent. As foreign matter, including smoke, is carried in with the inspired air, it deposits on this broad expanse of ever-moving mucous blanket. The blanket moves upward, pushed by the cilia, and, as it does so, it flows into an ever-narrowing streambed until, when it reaches the trachea, instead of being meters wide, it is only 5 cm. wide. From the trachea, it is carried through the larynx and into the esophagus. As the ciliary stream flows along continuously, it is continuously renewed by glands lying in the epithelium.

Like geographic rivers, this ciliary stream, as it flows along, meets certain obstructions. These consist of the openings of tributary bronchi, which must be by-passed, and, in many otherwise normal people, squamous or metaplastic islands which are devoid of cilia. As the stream flows along, it is presumably more or less retarded at such islands, and possibly also at bronchial openings, although this is less certain. The

*The total cross-sectional area of the tracheobronchial tree remains more or less constant down as far as bronchioles 1 mm. in diameter. Somewhere below that the cross-sectional area increases markedly, as well as the cumulative circumference.

direction of ciliary beat upstream from bronchial openings changes from an axial to an oblique or transverse direction in such manner as to facilitate manipulation of the mucous blanket about the opening. Nevertheless, a four-way split of the mucous blanket takes place at the upstream margin of the bronchial opening, with possibly some retardation occurring. At the anterior end of the vocal cords, there is also a splitting of the mucous blanket and, just beneath the cords, a change of direction of the ciliary beat. The mucous blanket ceases its axial progress at the level of the vocal cord; here, at the anterior commissure, it splits in two halves, each of which passes backward under the margin of the cord, dragging along the edge of the squamous epithelium on the cords. The cilia in the area just beneath the cords, instead of beating in an axial direction, beat up and back. Most of the mucous drainage eventually passes between the arytenoids.

Over non-ciliated islands or other points of retardation, any noxious material contained in the ciliary stream has a longer time to exert its effect on the underlying cells. It is thought that cancer of the lung begins in this way in these squamous islands. Cigarette smoke and other air pollutants are known to contain carcinogenic compounds. This "hot stuff" exposes all the cells of the whole lining as the ciliary stream carries it along, but, at points where the stream is retarded, it has a little longer time to produce its effect on the underlying cells.[6] This suggests an explanation for the location of carcinoma.

Cigarette smoke has the effect in isolated bits of ciliated epithelium[5] and in experimental animals[2] of slowing the ciliary beat or stopping it entirely—permanently or temporarily, depending upon the dose. This need not be from contained carcinogenic compounds—probably is not. It is probably due to other rapidly acting toxic materials, possibly nicotine. So, in addition to the local slowing of the ciliary stream from previously existing non-ciliated islands, it is quite possible that cigarette smoke may have the effect of slowing the ciliary stream more or less throughout its extent, thus enhancing the injurious effects of the cigarette tar on both ciliated and non-ciliated areas.

Distal to the origin of the ciliary stream in the respiratory bronchioles are found the alveolar duct, atrium, sacculus and alveolus. These areas are even greater in extent than the respiratory bronchioles of our ciliary stream and have been compared in size to a tennis court. What happens to material deposited in these regions where there are no cilia? Some carbon, for instance, becomes incorporated in the walls or is carried to regional lymph nodes. Mellors has demonstrated that cigarette tar is picked up by wandering pneumocytes, carried upward to the respiratory bronchioles, where the cells disintegrate, depositing the contained tar upon the mucous blanket, to be carried out with the ciliary stream.[7]

To recapitulate: Most inhaled foreign material is deposited in the anterior third of the nose. From there it is carried by ciliary action back and downward to the pharynx, where it is swallowed. Cigarette smoke by-passes the nose and is fed from the mouth into the clean stream of inspired air in the pharynx. It is diffusely deposited throughout the tracheobronchial tree—probably somewhat more heavily just inferior to the vocal cords and in the root of the lungs, also somewhat more heavily

proximally than distally. The area for deposition increases markedly as the air flows downward. Even if the deposit is somewhat heavier proximally, the total quantity deposited distally is probably much greater because of the much greater area distally. Deposition of the tar takes place in the mucous blanket; some of the gases are undoubtedly dissolved and absorbed more or less rapidly. The mucous blanket, motivated by the underlying cilia, constitutes the ciliary stream. Cilia are generally not found below the respiratory bronchioles; deposition occurring deep to these either remains in the alveolar and saccular walls, is carried to the regional lymph nodes, or is picked up by wandering pneumocytes and carried back up to the respiratory bronchioles, where it is deposited in the beginning ciliary stream. As the ciliary stream flows upward, it flows through an ever-narrowing streambed and it encounters certain obstructions—squamous islands, bronchial openings and the vocal cords. It is dragged over the non-ciliated spots by traction on the mucous blanket exerted by surrounding cilia. From the standpoint of physics, it would seem that there must be some degree of slowing at such islands.

Recent experiments indicate that cigarette smoke has the effect of slowing or temporarily stopping ciliary action. This would further enhance retardation of ciliary flow and correspondingly increase the destructive action of contained foreign compounds.

At the upstream margin of the bronchial openings a four-way split takes place and the mucous blanket is torn apart, but its motion is facilitated by obliquely-directed cilia around the rim of the opening. Something similar happens at the anterior commissure in the larynx; the mucous blanket is brought up from the anterior portion of the larynx to the level of the vocal cord and is split in the midline anteriorly to flow under the vocal cord and back to the interarytenoid area.

Carcinoma is thought to have its genesis in the squamous islands and in the squamous epithelium on the vocal cords, especially in the anterior third, where there is some retardation of flow. This might explain the fact that carcinoma rarely originates in the posterior part of the cords and might explain the recent findings of Multanen[8] that there is more activity in the anterior part of a carcinoma of the cord than in the posterior, as indicated by mitotic figures.

SUMMARY

1. Inhaled cigarette smoke by-passes the natural cleansing mechanism of the nose, to which most air pollutants are subjected. The tar droplets from the smoke are diffusely deposited in the mucous blanket throughout the tracheobronchial tree as the inspired air flows down. These deposits are somewhat heavier just under the vocal cords and in the root of the lungs than elsewhere. The greatest total quantity is deposited in the small bronchioles and alveoli.

2. The physiologic drainage of the bronchial tree is accomplished by the mucous blanket, which, motivated by the underlying cilia, constitutes the ciliary stream. From respiratory bronchioles to esophagus, the streambed narrows markedly and probably the velocity of flow of mucus increases as the stream-bed narrows. In its ever-narrowing course from respiratory bronchioles to esophagus, the ciliary stream encounters a number of naturally-occurring obstructions in the form of squamous islands, bronchial openings, and the squamous epithelium of the vocal cords. Retardation of the ciliary stream may occur at these areas and may be further enhanced in the presence of cigarette smoke, which slows or temporarily stops ciliary action. Thus, prolonged action of any carcinogen contained in the ciliary stream could occur at these spots.

3. The distribution of squamous-cell carcinoma in the respiratory tract suggests a relation to the ciliary streaming.

RESUMEN

1. El hubo inhalado al fumar cigarrillos sigue un camino desviado del natural que es la nariz que ejerce un papel de limpiado natural frente a la mayoría de las poluciones del aire.

Las gotitas de alquitrán del humo, se depositan difusamente sobre la cubierta mucosa en todo el árbol bronquial al ingresar el aire inspirado. Estos depósitos son algo mas densos exactamente debajo de las cuerdas vocales y en hilio pulmonar que en otras partes. La mayor cantidad total se deposita en los pequeños bronquiolos y alveolos.

2. La canalización fisiológica del árbol bronquial se realiza por la cubierta mucosa que bajo el influjo de las pestañas subyacentes promueven una corriente ciliar. De los bronquiolos al esófago el lecho de la corriente se estrecha notablemente y probablemente la velocidad de la corriente aumenta en razón de ese estrechamiento. En su siempre disminución de calibre de los bronquiolos al esófago, la corriente ciliar tropieza con ciertos obstáculos naturales en forma de islotres escamosos, aberturas bronquiales, y el epitelio escamoso de las cuerdas vocales. El retardo de la corriente ciliar puede ocurrir en estas áreas y puede acentuarse por la presencia del humo de cigarrillo el que también detiene temporalmente la acción ciliar. Así la acción prolongada de cualquier carcinógeno contenido en la corriente ciliar, puede effiercerse en esas áreas.

3. La distribución del carcinoma bronquigénico de celdillas escamosas en el conducto respiratorio, sugiere una relación con la corriente ciliar.

RESUMÉ

1. La fumée de cigarette inhalée traverse le système naturel d'épuration que constitue le nez, grâce auquel la plupart des facteurs de pollution de l'air sont arrêtés. Les goutelettes de goudron provenant de la fumée sont déposées de façon diffuse sur la muqueuse qui tapisse l'arbre trachéo-bronchique lorsque l'air y pénètre. Ces dépôts sont toutefois un peu plus denses sous les cordes vocales, et à la racine des poumons que partout ailleurs. La plus grande partie est déposée dans les petites bronchioles et alvéoles.

2. Le drainage physiologique de l'arbre bronchique est effectué par la muqueuse qui, mise en mouvement par les cils sousjacents, constitue le courant ciliaire. Des bronchioles respiratoires jusqu'à l'eosophage, ce courant se rétrécit d'une façon nette et probablement la rapidité du flot de mucus augmente à mesure qu'il se rétrécit. Dans sa course toujours plus étroits des bronchioles respiratoires à l'oesophage, le mouvement ciliaire rencontre un nombre d'obstacles naturels sous la forme d'ilôts squameux, des orifices bronchiques et de l'épithélium squameux des cordes vocales. Le retardement du mouvement ciliaire peut survenir dans ces zones et peut être ultérieursement amplifié par la présence de fumée de cigarette, qui ralentit ou arrête momentanément l'action ciliaire. Alors, l'action prolongée d'un carcinogène contenu dans le tapis ciliaire peut survenir en ces points.

3. La localisation des cancers épidermoïdes dans l'arbre respiratoire suggère une relation avec le mouvement ciliaire.

ZUSAMMENFASSUNG

1. Inhalierter Zigarettenrauch schließt den natürlichen Reinigungsmechanismus der Nase kurz, dem der größte Teil der stoffe unterworfen ist, die die Luft verunreinigen. Die Teertrípfchen, aus dem Rauch werden in diffuser Form über die Schleimschicht des ganzen Tracheobronchialbaumes ausgebreitet in dem Maße, wie die eingeatmete Luft nach abwärts gelangt. Diese Ablagerungen sind etwas ergiebiger unmittelbar unterhalb der Stimmbänder und an den Lungenwurzeln als anderwärts. Die größte Gesamtmenge wird in den kleinen Bronchiolen und Alveolen abgelagert.

2. Die physiologische Drainage des Bronchialbaumes wird durch die Schleimschicht bewirkt, die aufgrund der unter ihr befindlichen. Flimmerhaare den Flimmerstrom zustande bringt. Von den respiratorischen Bronchiolen bis zum Oesophagus verengert sich das Strombett merklich, und wahrscheinlich nimmt die Geschwindigkeit des Schleimflusses in dem Maße zu, wie sich das Strombett verengt. Auf seinem ständig schmäler werdenden Weg von den respiratorischen Bronchiolen bis zum Oesophagus trifft der Feimmerstrom auf eine Anzahl natürlich vorkommender Hindernisse in Form versprengter Plattenzellen, Bronchialöffnungen und der Plattenepithel der Stimmbänder. Eine Verzögerung des Flimmerstromes kann in diesen Bereichen auftreten und kann noch weiter verstärkt werden durch die Anwesenheit von Zigarettenrauch, der die Flimmertätigkeit verlangsamt oder vorübergehend abstoppt. So kann es zu einer verlängerten Einwirkung eines im Flimmerstrom enthaltenden carzinogenen Stoffes an diesen Stellen kommen.

3. Das Vorkommen von Plattenepithel-Zellcarzinomen im Bereich der Atmungsorgane legt eine Beziehung zu dem Flimmerstrom nahe.

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ADAMS-STOKES SYNDROME DURING NORMAL SINUS RHYTHM AND TRANSIENT HEART BLOCK

A study was made of the effects of carotid sinus digital pressure and deep breathing on ten patients who were subject to Adams-Stokes seizures during normal sinus rhythm and transient heart block.

The paradoxical development of sinus rhythm following carotid sinus pressure and deep breathing in such patients may be attributed in part to: (1) an improvement in A-V conduction through a slowing of the atrial rate; (2) the liberation of epinephrine following compensatory vasoconstriction after a transient drop in blood pressure due to carotid sinus reflexes; (3) a change in the pacemaker of the heart as a result of the appearance of a well-timed extrasystole when a slower rhythm can be converted to a more rapid one; and finally, (4) to the building up of impulse formation with escape of the sinus pacemaker during induced standstill of the whole heart.

The unpredictable alterations in the cardiac mechanisms resulting from such changes are in part responsible for the difficulties encountered in the treatment and prevention of ventricular asystole in such patients.

Schwartz, S. P., and Schwartz, L. S.: "Adams-Stokes Syndrome during Normal Sinus Rhythm and Transient Heart Block; III. The Paradoxical Effects of Carotid Sinus Digital Pressure and Deep Breathing on Patients with Adams-Stokes Seizures during Normal Sinus Rhythm and Transient Heart Block," *Am. J. Cardiol.*, VII:204, 1961.

ANEURYSM OF THE RIGHT PULMONARY ARTERY IN A PATIENT WITH ATRIAL SEPTAL DEFECT CAUSING RIGHT MIDDLE LOBE COLLAPSE

Pulmonary artery aneurysms carry a poor prognosis. Sudden death may be caused by rupture. Surgery should be considered in the management of this condition. If there is a causal congenital heart defect, then this should be investigated and treated if possible. Repair of the atrial septal defect in our case reduced the size of the aneurysmal dilatation of the pulmonary artery and removed the pressure from the right bronchus intermedius. Danger of rupture was correspondingly reduced, and we hope the patient will have fewer attacks of prulent bronchitis and no further episodes of right middle lobe collapse or infection. If a direct attack on such an aneurysm was contemplated, angiocardiography would be a useful preoperative investigation.

Sloman, G., and McConchie, I. H.: "Aneurysm of the Right Pulmonary Artery in a Patient with Atrial Septal Defect Causing Right Middle Lobe Collapse," *Med. J. Austral.*, II:577, 1960.

Physiologic Auto-Control of Mechanical Respirators*†

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We have all long appreciated the superior nature of the biochemical and physiologic processes of the body for the inherent control of many of the organisms' basic functions. It has previously been impossible to substitute a machine for the function of a physiologic process and maintain any degree of normality.

This problem of mechanical substitution has been especially prevalent in the field of mechanical respirators. The present commercial units tend to hyperventilate or hypoventilate the individual. In the acutely ill patient the units must fatigue the patient into submission to take over total ventilatory function. In patients with chronic respiratory insufficiency the individual must learn to relax completely and make no muscular effort. Both of the foregoing methods are objectional, the former from the exhaustion of the patient and the latter from lack of muscular contraction which is necessary to strengthen and develop accessory muscles in an attempt to return basal respiratory function.

Recognizing the above difficulties and appreciating the advantage of the normal body responses to control extracorporeal units, an electronic respirator control was developed by Montgomery at our institution. This unit, previously described,[1,2,3] detects and amplifies the electrical potential of a contracting muscle and utilizes this potential to activate a respiratory aid. This then synchronizes the patient's efforts to breathe and the ventilatory efforts of the respirator. The patient has complete control of each breath both as to timing and depth.

Over the last two years this unit has been evaluated on approximately 100 animals and on 17 humans. The results have been most encouraging and form the basis of this report.

Description of Unit

The electrical potential generated by contracting muscles are complex pulses from 1.0 to 1000 microvolts with a du' 'ion of from 0.01 second to approximately 1 millisecond when recorde. 'm the surface. These impulses can be detected with either concentric needle electrodes or nickel-silver disk electrodes. The greatest problem to overcome is an electronic instrument that will monitor these minute potentials from artifacts which arise from strong 60 cycle per second power fields and the stronger potential generated by the myocardium. The control unit utilizes the differential duration of these impulses for satisfactory operation since the striated muscle potentials have a duration of a few milliseconds compared to the heart and other artifacts whose impulse durations are usually less than 1/100 of a second.

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The control unit uses an amplifier with a low frequency cut-off near 100 cycles. The input stage is push-pull in type and has a high value of common cathode resistance to cause degeneration of in phase voltages. Interstage coupling transformers are tuned to pass 100 to 1000 cycles per second. The tuning of the third stage input transformer is made variable by using a tap switch and fixed capacitors which range from 0.0001 to 0.025 microfarads. A slight amount of positive feedback is used to increase the apparent Q of this stage.

Adjustments necessary to use the electronic control unit have been made and kept simple since the application clinically is usually made by nurses, practical nurses, technicians or members of the patient's family. As a measure of simplicity, one patient using the unit on a home basis now has her 15 year old brother applying the unit.

There are three controls (Fig. 1), only one of which may need adjustment during any particular run. A balance control is present for original application and this then remains stable as does the frequency selector switch. The attenuator control dial may need minor adjustments if the unit is used continuously for prolonged periods of time.

By making minor adjustments on any commercial respirator, the unit can be attached for satisfactory performance with adequate safety measures for switching back to timed cycling. The unit has been used satis-

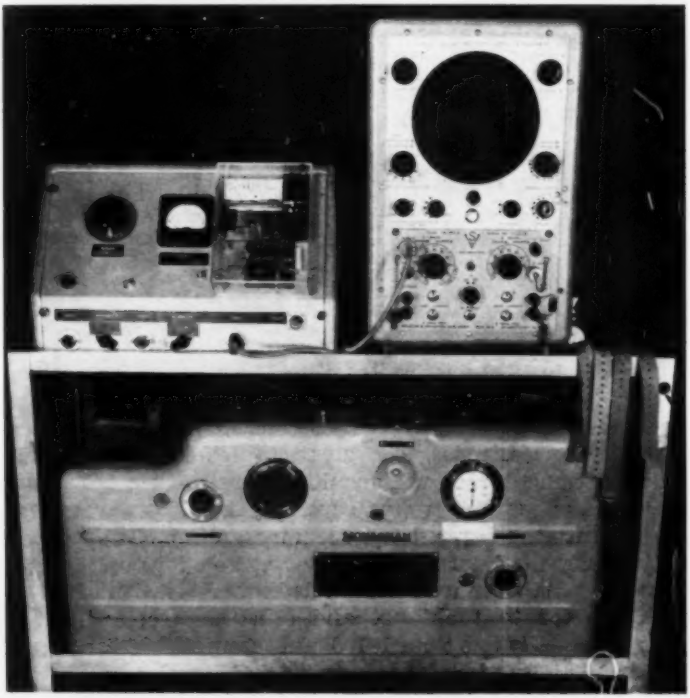

FIGURE 1: Electronic respirator control (upper left) with monitoring oscilloscope and attached to activate a Monaghan blower. The attenuator dial is usually the only variable to be adjusted.

factorily with tank respirators, chest shell respirators, endotracheal positive pressure insufflation, tracheostomy insufflation and oral insufflation.

Methods

The procedures must by necessity be divided into two component parts, the experimental and clinical. The experimental evaluation of the unit has been described previously,[4] but since this appeared in an European journal, some aspects will be included.

Dogs suffering from chronic respiratory insufficiency, resulting from staged bilateral division of the phrenic nerves, were anesthetized and attached to the respirator control. The impulse was obtained from a needle electrode placed in the ali nasalis. The animal then was allowed to assist his respiratory efforts by utilizing the respiratory control activating a Monaghan blower attached by a suitable valve to the endotracheal tube. Measurements of the arterial pH, pCO_2, and O_2 saturation were made at frequent intervals up to four hours. Another group of animals was subjected to acute bilateral thoracotomy and simultaneous division of both phrenic nerves and were attached to the respirator in a similar fashion. This latter group was then totally dependent on the respirator for the maintenance of respiratory activity. Similar studies were obtained on these animals for periods up to five hours.

Encouraged by the slight deviation from normal encountered from the animal experiments over prolonged periods of time we have utilized the electronic respirator control on 17 post bulbar poliomyelitis patients from the regional Respiratory and Rehabilitation Center for a total time in excess of 900 patient hours. These clinical applications were, for the sake of convenience and patient comfort, monitored for vital capacity changes rather than arterial blood studies. The electronic pickup on these patients was obtained from an active remaining intercostal muscle

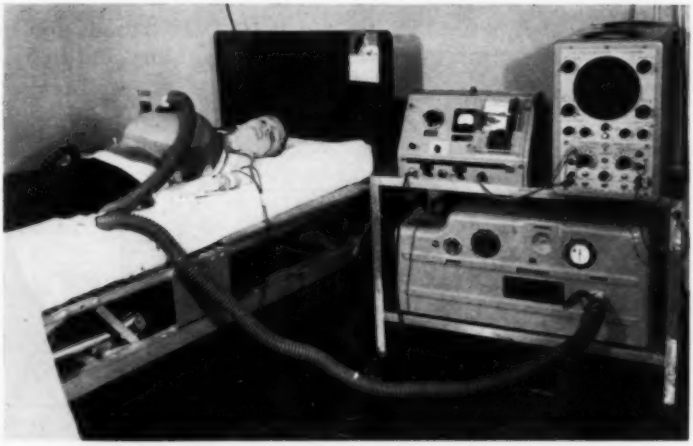

FIGURE 2: Unit attached to patient with chest shell. The indifferent and ground electrodes are attached to the patient's left arm and the active electrode is over the sternocleidomastoid muscle.

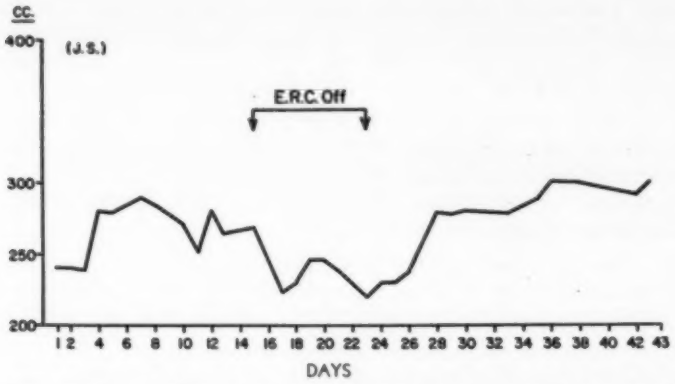

FIGURE 3: Vital capacities on 28 year-old white man. The ERC was attached on the third day with improvement. The table also demonstrates the reduced respiratory function when a conventional tank was substituted with subsequent improvement.

or an accessory muscle of respiration which had been developed by the individual patient (Fig. 2). In most instances these are comprised of the platysma, sternocleidomastoid, pectoralis major or temporal muscles. The electrodes used are standard electrocardiographic plates applied with electrode plast. Experience has shown that these electrodes may stay in place without the fear of contact failure for as long as 72 hours.

Results

The animal experiments demonstrated the relative safety of the unit and its dependability for unattended use. The mean change in pCO_2 of +3 mm., after three hours use in the chronic animals and the change of −3 mm. in the acute animals seems well within tolerance as did the pH changes of +.007 and +.004 respectively. Oxygen saturation at first appeared to be low but repeated observation and attempts to enrich the oxygen atmosphere proved these values to be acceptable.[5]

We have been well pleased with the results of the patient application of the unit. In our endeavors as a Regional Respiratory and Rehabilita-

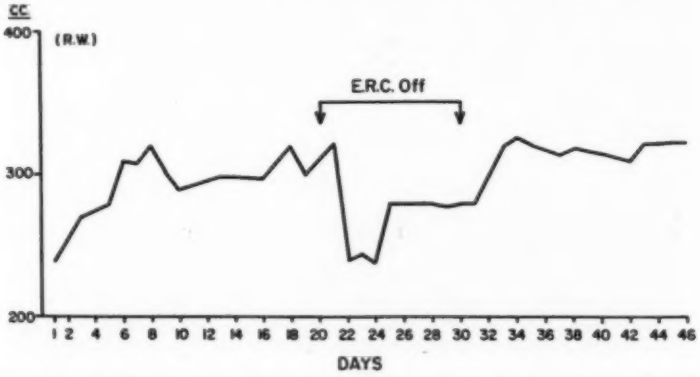

FIGURE 4: Similar changes occur in a 19 year-old white woman, but this also demonstrates the plateauing effect. This patient was weaned from all respiratory aids.

tion Center, many opportunities present in the line of difficult problems of artificial ventilation. The conventional methods for prolonged artificial ventilation at this time have the primary objection of delivering a fixed tidal volume at a fixed rate regardless of patient demand. The common error with this type of ventilation is usually hyperventilation which may prove deleterious.[6] The electronic control unit was evaluated to test whether the body's own physiologic and biochemical needs were satisfactory to control the rate and volume of a conventional respirator.

From June, 1957, until the present time, the device has been used on seventeen different patients suffering the residua of bulbar poliomyelitis. All of these patients have been totally or partially dependent on some sort of mechanical ventilatory aid. When possible the electronic control triggered device was substituted entirely for other aids. The tidal volume of these patients ranged from 25 cubic centimeters to 150 cubic centimeters of air.

The unit has now been used in excess of 900 patient hours with no untoward results. Tidal volumes before use, after use of the respirator control, and for prolonged periods after use have been obtained by us and by independent observers (Department of Physical Therapy). These measurements have been found to correlate closely and always to follow the same trend. In some patients, use of the new machine was interrupted, replaced for a time with a conventional respirator, and the unit then reattached.

Several interesting observations have been made on this group of patients. It was observed without exception that the patients maintained a slower respiratory rate when each attempt to breathe was augmented rather than ignored by their ventilatory aid. This rate was slower than their previous mechanical respirator had been triggered and also slower

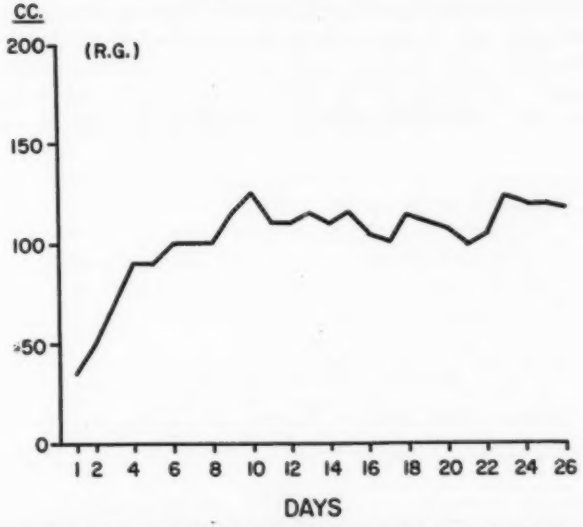

FIGURE 5: Twenty-seven year-old white woman who has now been weaned from the tank and is using the electronic control attached to a chest shell for two hours daily.

than their rate during free breathing as would be expected. The decreased rate was associated with an increased tidal volume since the patient controls the depth of each breath by the strength of muscular contraction. It was also noted consistently that these patients demonstrated an increase in tidal volume after using the respirator control. These values would stay at 2 to 3 times pre-testing levels for as long as 5 to 6 hours after use of the instrument in some cases and take up to 24 hours to slowly return to their previous levels.

When individuals are subjected to daily use of the device we have found that the vital capacity tends to "plateau." If the unit is discontinued and a conventional respirator substituted, these levels again drop back toward their original base line.

Figures 3 to 6 show segments of four individual patients' records. A study of these tables brings out certain points previously mentioned. One sees the poor original function of all patients and a marked improvement coincident with the use of the electronic respirator control. The plateauing effect of continued use is evident as is the deterioration when use of the instrument is stopped. A prompt recovery occurs when the use of the unit is reinstituted.

Sixteen of the 17 patients on whom we have tested the unit have volunteered their preference for this new type of respiratory aid. The other patient had no objection, but stated he could note no improvement. We feel that the unit has been instrumental in weaning eight of these patients from all respiratory aids and in facilitating their discharge from the hospital free breathing. One additional patient is using a unit at home for two hours a day. This patient is of considerable interest. For the five preceding winters she has spent about 80 per cent of the cold months in the Center with various episodes of pneumonia and atelectasis. For the first winter since she contracted polio it has been unnecessary to admit her to the hospital. She is, however, our longest continuous user and whether this will be observed in other patients is difficult to predict.

The individual patients volunteer many other advantages to this type of respiratory assistance. These patients by controlling their own respirators can eat and drink without the strict timing of the cycle to

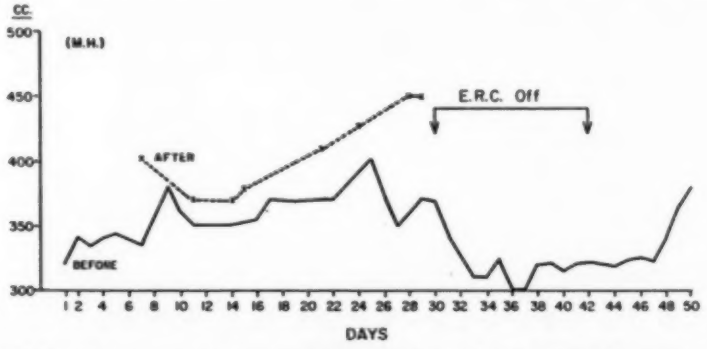

FIGURE 6: Measurements taken on a young engineer showing the difference in daily vital capacities before applying the respirator control and two hours after it was discontinued.

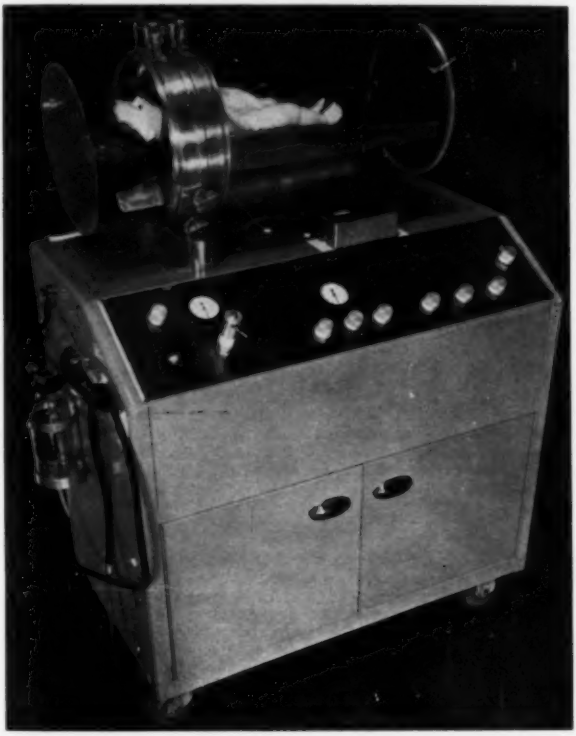

FIGURE 7: Transistorized unit attached to new premature or infant tank respirator.

prevent aspiration, they can talk and carry on a more normal conversation, they are more mobile for physio-therapy, and they do not suffer as much apprehension since they feel that if they need a deep breath, they can take one.

It is only proper that certain limiting factors of the unit should be pointed out. Surface electrode use is not applicable on patients who use their diaphragm as their main respiratory muscle or on those who free breathe by the glosso-pharyngeal method. Studies with needle electrodes, however, are promising in the former group. Another limiting factor is that some patients utilize accessory muscles to activate the unit and this makes use during sleep hazardous. If the individual is using a primary or secondary muscle to activate the unit sleep is possible with safety.

SUMMARY

Preliminary studies are presented concerning a new approach to artificial control of mechanical respirators. The experimental and clinical results of this method have been gratifying. The development of the muscle potential amplifier as used to control the respirators has opened up other fields of endeavor. Some of the more important applications now under investigation are:

(1) The adaption to control a mechanical respirator for premature and newborn infants (Fig. 7). This is being evaluated in prematures and infants with hyalin membrane disease.

(2) For internal stabilization of a flail chest or one exhibiting paradoxical motion.

(3) To control an extracardiac stimulator in cases of complete heart block by utilizing the auricular p wave to trigger such a device.[7]

(4) To control the contraction of the McKibbon artificial muscle.

The respirator as now used appears to maintain more normal respiratory function than previous units have been capable of doing. We definitely feel that the control of mechanical insufflators by the patient's own biochemical and physiological needs is in every instance desirable if practical.

RESUMEN

Se presentan estudios preliminares en relación a un nuevo modo de considerar el control artificial de los respiradores mecánicos. Los resultados experimentales y clínicos del método han sido satisfactorios. El desarrollo del potencial muscular de amplificación como se usa para controlar los respiradores, ha abierto otros caminos de posibilidades. Algunas de las mas importantes aplicaciones se encuentran en estudio, como son:

(1) La adaptación al control de un respirador mecánico para los infantes prematuros (Fig. 7). Esta se esté ensayando en los reciennacidos prematuros y en los infantes con la enfermedad de la membrana hialina.

(2) Para la estabilización interna de un tórax de pared blanda o en el que tiene respiración paradójica.

(3) Para controlar u nestimulador extracardiaco en casos de bloqueo cardiaco completo usando la onda p auticular para desencadenar el mecanismo.[7]

(4) Para el control de la contracción del músculo artificial de McKibbon. El respirador como se usa ahora parece mantener mas la función respiratoria normal que lo logrado por otras unidades anteriores. Creemos decididamente que el control de los insufladores mecánicos por las propias necesidades bioquímicas fisiológicas del enfermo es en todo caso lo deseable y práctico.

RESUMÉ

L'auteur présente des études préliminaires concernant une nouvelle tentative de contrôle artificiel du mécanisme respiratoire. Les résultats expérimentaux et cliniques de cette méthode ont été satisfaisants. Le développement de l'amplificateur du potentiel musculaire utilisé pour contrôler les respirateurs a ouvert d'autres champs d'expérience. Quelquesunes des applications les plus importantes en cours d'étude sont:

(1) l'adaptation d'un respirateur mécanique pour les prématurés et les nouveaux-nés. Il est en expérimentation chez les prématurés et les nouveaux-nés atteints de la maladie de la membrane hyaline;

(2) pour la stabilisation interne d'un thorax ne se trouvant pas sous contrôle musculaire ou faisant preuve d'un mouvement paradoxal;

(3) pour contrôler un stimulateur extracardiaque dans les cas de bloc cardiaque complet en utilisant l'onde auriculaire pour se déclencher comme un ressort;

(4) pour contrôler la contraction du muscle artificiel de McKibbon.

Le respirateur, comme il est utilisé actuellement semble maintenir une fonction respiratoire plus normale que les appareils antérieurs n'ont été capables de le faire. Nous sentons nettement que le contrôle des insufflateurs mécaniques par les besoins biochimiques et physiologiques du malade luiméme est dans tous les cas souhaitable s'il est réalisable.

ZUSAMMENFASSUNG

Es werden vorläufige Untersuchungen vorgelegt, die eine neue Möglichkeit der künstlichen Überwachung mechanischer Respiratoren betreffen. Die experimentellen und klinischen Ergebnisse dieses Verfahrens waren zufriedenstellend. Die Entwicklung des Muskel-Potential-Verstärkers in seiner Form zur Überwachung der Respiratoren hat auch noch andere Anwendungsbereiche ermöglicht. Einige der wichtigeren z.Zt. in Erprobung befindlichen Gebiete sind:

(1) Anpassung zur Überwachung für einen mechanischen Respirator für Frühgeburt und Neugeborene (Fig. 7). Ferner wird er erprobt für Frühgeburten und Säuglinge mit Erkrankung der hyalinen Membran.

(2) Zur innerlichen Stabilisierung einer Flachbrust oder bei paradoxer Thoraxbewegung.

(3) Zur Überwachung eines extracardialen Stimulators in Fällen von komplettem Herzblock durch Benutzung der Vorhofs-p-Zacke, um eine solche Vorrichtung auszulösen.[7]

(4) Zur Überwachung der Kontraktion des künstlichen McKibbon-Muskels.

Der jetzt gebräuchliche Respirator scheint eine mehr dem Normalen entsprechende Atemfunktion zu gewährleisten, als es frühere Einheiten vermochten. Wir sind der festen Überzeugung, daß die Überwachung der mechanischen Zersteuber durch die biochemischen und physiologischen Bedürfnisse des Patienten selbst in jedem Fall wünschenswert ist, sofern sie sich durchführen läßt.

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PLASTIC BRONCHITIS

Plastic bronchitis is one of the rarer bronchial diseases and there have been only about 300 cases in the world's literature, most of them in the nineteenth century. It is also described as fibrinous, pseudo-membranous, or Hoffman's bronchitis, or as bronchial croup. The formation of the characteristic mucous plugs can usually be traced to a combination of factors. Moderate inflammatory change in the bronchial wall is the most constant of these which may include congestion and edema of the mucosa, sometimes with hemorrhage, and infiltration by polymorphonuclear leucocytes, eosinophils, or lymphocytes, extending into the deeper layers. Clinical signs of infection include fever, cough with yellowish sputum, and leucocytosis. The bacteria found in the bronchial tree or expectorated in plastic bronchitis are inconstant and not of specific etiologic significance. Occasionally, the immediate cause of the bronchial irritation may be physical (as by inhalation of dust or smoke) rather than bacteriologic, though these two factors may act together. A further precipitating factor may be an allergy.

In general, the prognosis is good, recovery from an attack usually occurring spontaneously, though the patient may be very ill and greatly distressed for several days. The prognosis is worse at the extremes of life.

In mild cases, the warm moistened air of steam inhalations may give sufficient relief of a trypsin aerosol may be tried and these measures should be combined with postural coughing and percussion. Where bronchospasm is present, adrenalin and other antispasmodics may be of benefit and corticosteroids may be helpful especially where there is a history of asthma (Pilgerstorfer, 1956). Antibacterial drugs should be given to combat infection in the collapsed lung. In all severe cases, bronchoscopic aspiration should be carried out at the earliest opportunity for by this means only can an exact diagnosis and assessment be made and speedy relief of bronchial obstruction obtained.

Johnson, R. S., and Sita-Lumsden, E. G.: "Plastic Bronchitis," *Thorax*, 15:352, 1960.

INTRACARDIAC MYXOMAS AND THROMBI

Cardiac tumors are relatively infrequent lesions which have assumed clinical importance as successful methods for intracardiac surgery have been developed. To date, approximately 550 primary tumors of the heart have been reported. Over 300 have been myxomas. This tumor typically arises from the atrial septum in the region of the fossa ovalis. It is three times more frequent in the left atrium than in the right.

Intracardiac tumors may occur at any age. The majority have developed in patients between the ages of 30 and 60 years. The incidence has been greater in women. The usual clinical manifestations arise from obstruction of the mitral or tricuspid valve. In recent years, angiocardiography has resolved many of the difficulties inherent in establishing an accurate preoperative diagnosis.

Now that successful surgical methods for removal of these lesions are available, early clinical recognition is important.

Adams, C. W., Collins, H. A., Dummit, E. S., and Allen, J. H.: "Intracardiac Myxomas and Thrombi," *Am. J. Cardiol.*, VII:176, 1961.

Is Serious Pulmonary Disease Caused by Nonphotochromogenic ("Atypical") Acid-Fast Mycobacteria Communicable?*

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Rome, Georgia

It is indeed an honor to be invited to speak to you on this occasion. The many local, national and international honors already conferred upon Dr. Waksman for his many scientific contributions to the welfare of humanity are revealed in the almost innumerable citations in his biography.

I am happy to have a part in perpetuating the recognition of Dr. Waksman's many accomplishments, and, in so doing, I would like to talk to you on a subject which needs extensive research. We need to know the source of an infection of the lungs by certain acid-fast mycobacteria and to know if these organisms are communicated from person to person. Furthermore, there is great need for more effective drugs than are now available for treating this infection when it becomes pathogenic to man. We sincerely hope that Dr. Waksman can make another important contribution to medicine by discovering the answers to these problems.

For several years there has been a need for epidemiological studies, particularly in some of the southeastern states, in regard to a serious pulmonary disease caused by one of the several strains of *"atypical"* acid-fast bacilli. The need for this study is not because of a high prevalence of the disease, but because the source of these organisms and the manner in which man becomes infected with them are unknown. The known incidence of disease in Georgia is low, as only about 1 per cent of 15,180 patients admitted to our tuberculosis hospital during the past 10 years had demonstrable pulmonary lesions associated with these mycobacteria in the sputum.

In a previous report it was pointed out that of 69 patients, the sputum cultures of 64 grew out the same strain of *"atypical"* organisms.[1] The cultures of the 64 strains were smooth, moist, slightly chromogenic, slow-growing, dysgonic in appearance at the end of six weeks and not subject to appreciable color change when exposed to light.

According to Runyon,[2] these strains were characterized, in part at least, as nonphotochromogenic acid-fast mycobacteria, Group III. For the most part they were nonpathogenic to the guinea pig.

In our previous report it was pointed out that only 17 per cent of the patients were under the age of 40, whereas 50 per cent of all tuberculous patients admitted to the hospital during the preceding five years were under 40. Many of the patients had had repeated episodes of respiratory illness, and 59 per cent were white men. Forty-one per cent of all tuberculous patients admitted during the period were Negroes, but only 13

*Selman Waksman Lecture, New Jersey Chapter, American College of Chest Physicians.

**From Battey State Hospital, Rome, Georgia.

per cent of the 69 patients were of this race. There were 63 married patients, but no spouse had ever had tuberculosis. No two patients had ever been discovered in the same family or among household contacts. Surgically resected materials of pulmonary lesions of seven patients were grossly and microscopically indistinguishable from tuberculosis. Only 68 per cent were positive reactors to first strength OT, and only 29 per cent of 122 family or household contacts tested by the health departments[3,4] were found to be positive to the same dose. At that time most of the reactors that were considered positive were read in terms of plus 1, 2, 3 or 4. Plus 1 was equivalent to a measured induration of more than 5, but not exceeding 10 mm. induration, etc., in accordance with NTA standards. Such terms will subsequently be used in stating the results of tests with OT or PPD among additional contacts.

Some of the foregoing observations raised the question of communicability of this disease and, since it was shown that 70 per cent of the patients remained sputum positive under chemotherapy, a clinical as well as a potential epidemiological problem was encountered.

Since that report was made, 104 additional patients have been admitted with *"atypical"* acid-fast mycobacteria in the sputa. Of the 104, the cultured sputa of 94 grew out only nonphotochromogens. Without going into detail it can safely be said that the age, sex, race, history, the

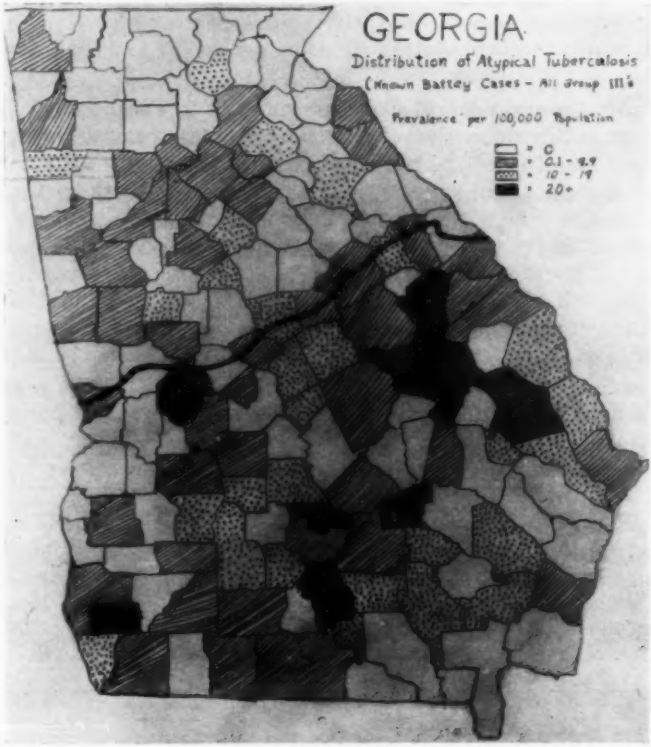

FIGURE 1

tuberculin reaction and other clinical features of the 94 patients fell into the same pattern as the 64 previously reported, making a total of 158. Additional information has been gathered, however, on 95 patients of both groups regarding all previous occupations and it was found that 81 per cent had, at one time or another, lived on farms. Of the two groups, 152 were married or widowed. One, a 76 year old widowed white woman, said that her husband had died of tuberculosis years ago. He was never hospitalized and there was no bacteriologic or roentgenographic confirmation of the diagnosis. Otherwise, there has been no history of tuberculosis in the spouse among the other married or widowed patients.

The majority of the 158 patients were over 60 years of age. There might be some question if the low incidence of a significant tuberculin reaction could be attributed to age. However, none was so acutely ill from pulmonary disease to be anergic. Moreover, the majority who were negative were between the ages of 50 and 59.

Figure 1[5] shows the prevalence of disease by counties in the state. It will be noted that the state is divided into two areas by a somewhat diagonal line crossing from west to east, and is known as the Fall Line. The northern area is mostly mountainous or hilly, while the southern area is, for the most part, rolling or flat. The white or unshaded counties denote that no patient has been admitted from such counties. The cross-hatched counties denote that the prevalence is 0.1-9.9 patients per 100,000 population; the dotted counties denote 10 to 19, and the black areas denote 20+ per 100,000.

Although there are no blacked-out counties in the northern portion, the largest and perhaps the most densely populated counties in the state are in two counties of the northern portion, but each of these counties shows a prevalence of only 1.9 per 100,000 in contrast to 10 to 30 in some of the southern, mostly rural counties. It is found from a map furnished us by the Georgia Division of Mines, Mining and Geology, that the greatest incidence of this disease has been found in counties where the surface soil is fine, grain-size silica, and is classified as "Hawthorne" soil (sedimentary rocks). Practically all of this type of soil is found below the Fall Line.

Pretreatment susceptibility studies of these organisms to streptomycin were done on 81 patient strains of the 94 patients previously mentioned.

TABLE 1—REACTION TO PPD-S AND PPD-B AMONG 51 PATIENTS

	Patients
Non-reactors to both antigens	2
To PPD-S alone	
(a) 6 mm. or over	3
(b) Under 6 mm.	2
To PPD-B alone	
(a) 6 mm. or over	16
(b) Under 6 mm.	1
Six mm. or over to B, under 6 to S	3
Six mm. or more to S and B	24
Total	51

Of this number 58 were sensitive, 23 partially resistant and none completely resistant. A growth of 10 mcg./ml. comparable with the control was considered to be complete *in vitro* resistant. Studies of susceptibility to INH were done on strains of 80 patients prior to treatment. All 80 had growth on 1 mcg./ml. comparable with the control, indicating complete *in vitro* resistance.

Response to streptomycin plus PAS, INH plus PAS, or, to all three drugs given simultaneously has been equally as poor among the latter as the former group of patients, thus, again, posing a possible potential epidemiological problem.

One hundred seventy-three patients are mentioned in the abstract furnished for this program. However, the sputum of 15 patients, five of the first group and 10 of the second group, either produced different strains of *"atypical"* organisms, or both group III *"atypical"* and *M. tuberculosis* were concurrently or alternately isolated. (One patient converted from *"typical"* to *"atypical"* and one from *"atypical"* to *"typical"*). After submitting the abstract it was decided to withhold at this time discussion of these patients and their contacts because of the need for individualization of the patients and further studies of the contacts.

This has been a very limited study in epidemiology of this disease. For the lack of much needed research to establish the source and mode of transmission of infection, the study, of necessity, had to be limited to the clinical aspects of the patients; the tuberculin reaction to OT or PPD among household contacts; the reaction of patients and contacts to an antigen prepared from a nonphotochromogenic strain obtained from a patient in the hospital; a re-evaluation of the geographic distribution of this disease in Georgia, since our previous report, and a continuing search for a contact case.

In order to illustrate some of the features of this disease and the findings among contacts, the following case history is presented (Fig. 2). This is the chest x-ray film of a white man, 39 years of age, when first admitted in December, 1955. It is felt that roentgenographically these lesions are indistinguishable from pulmonary tuberculosis (however, in many patients the location of the lesion, or lesions, and the extensive amount of fibrosis and emphysema are not necessarily considered characteristic of tuberculosis). No mycobacteria or fungi have at any time been isolated from the sputa of this patient except nonphotochromogens. He had had symptoms suggestive of tuberculosis for about one and one-half years prior to admission. His family and marital history were negative for tuberculosis and there was no known contact with the disease. Other than chest findings and being underweight, the physical examination was not remarkable. At the time of his admission, his wife said that she and their six minor children had continuously lived in the home with the patient, and that he had been coughing for over a year. She stated

TABLE 2—NUMBER AND PER CENT OF 51 PATIENTS WITH 6 MM. OR MORE INDURATION

	Patients	Per cent
To PPD-S	28	55
To PPD-B	43	84

that she and all the children were tested with tuberculin and had x-ray films by the health department, shortly after the husband was found to have pulmonary disease, and they were all negative to both tuberculin and chest x-ray film inspection. Guinea pig inoculation was done with raw sputum from the patient and when the animal was sacrificed, it was considered to be grossly non-infected. However, a macerated portion of the spleen planted on culture grew out the same atypical organisms as originally isolated. Pretreatment drug susceptibility evaluation showed complete sensitivity to streptomycin and a 4+ growth on 1 mcg./ml. of INH. He has had streptomycin, PAS, INH, viomycin and cycloserine in various combinations, but no PZA because of slight abnormal liver function at the time the drug was considered. He has never been considered a surgical candidate. His sputum cultures remain positive. Figure 3 shows progressive disease and the prognosis would seem to be hopeless.

Information furnished us by the local health departments and the Division of Tuberculosis Control[3,4] showed that 336 household contacts of the 94 patients had been skin tested with first or intermediate strength OT or PPD. The results of those who were given 250 TU were excluded from this study because of the question of cross reaction if positive. Only 87 (26 per cent) were positive by the criteria of plus 1, 2, 3 or 4. This compares favorably with the 29 per cent of 122 contacts previously mentioned.

During our early observations of the clinical aspects of these patients and the low rate of tuberculin sensitivity to OT or PPD among them and their contacts, it became desirous to have an antigen prepared from the nonphotochromogenic strains to be used for tuberculin testing of patients and their household contacts. The purpose was for correlating the results with those usually found among *"typical"* cases of tubercu-

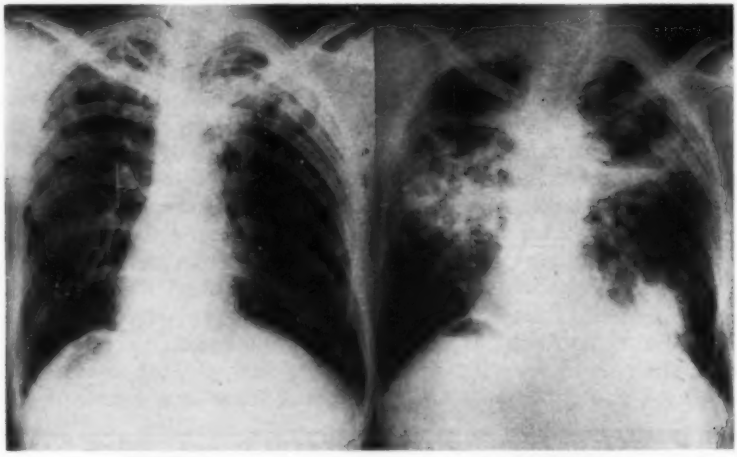

FIGURE 2 FIGURE 3

FIGURE 2: Chest roentgenogram on admission to hospital, showing bilateral infiltration with cavitary disease in each apex. FIGURE 3: Chest roentgenogram made approximately 50 months after admission, showing progressive infiltration and cavitary disease.

losis and their household contacts when tuberculin tested with OT or PPD. It was anticipated that should infection with these *"atypical"* organisms occur by reason of contact then the frequency of positive reactors among household contacts, when tested with an homologous antigen, should be similar to that usually found among household contacts of known *"typical"* cases of tuberculosis when tested with an homologous antigen, that of *M. tuberculosis*.

Drs. Florence Seibert and Lewis Affronti of Phipp's Institute were furnished cultures obtained from the sputum of patients in Battey Hospital, and they were kind enough to prepare antigens from two of these strains, known as Battey I and Battey II. Only the antigen prepared from Battey I, and referred to as PPD-B, was used in this study.

Beginning in September, 1958, a sufficient amount of this antigen, along with the standard PPD, prepared by Dr. Seibert and referred to as PPD-S, was obtained, as needed, to begin skin testing all patients admitted to the hospital. The dose of each antigen was 0.0001 mg., or 5 TU. The results of these tests are being studied by some of the staff, but are incomplete. (As a progress note it can be said, however, that among hundreds of tuberculous patients tested, the incidence of a 6 mm. or more induration to PPD-B among Negro patients had been considerably higher, thus far, than among white patients).

So far, 51 patients with *"atypical"* tuberculosis, including several discharged before this antigen was obtained, have been simultaneously tested with these two antigens. The criterion used to indicate a positive reaction was 6 or more millimeters of measured induration (Table 1). For convenience the letters, S and B, are used to indicate PPD-S and PPD-B, respectively. Table 2 shows the number and per cent who had a 6 mm. or more induration to S and B. Table 3 shows a comparison of induration among these patients.

Two hundred ninety-six of approximately 500 known household contacts of these patients have been tested with the same dose (5 TU) of the two antigens. Circumstances beyond our control made it impossible to test all contacts at this time. Two sets of tuberculin syringes and needles were used, one for PPD-S and one for PPD-B. At no time was there any mixing of the sets. They were sterilized in separate sterilizers and packaged separately. The antigens were given simultaneously in opposite arms. The criterion used for a positive reaction was the same as that used among patients. Table 4 shows the results of these tests among contacts of all ages, sex and race. Of these, four had the same number of millimeters, 16 had a greater reaction to S than B, and 15 had a greater reaction to B than to S. It was found that the total number that had 6 or more millimeters induration to PPD-B was 103, or 35 per cent,

TABLE 3—COMPARISON OF INDURATION AMONG 51 PATIENTS

	Patients	Per cent
Greater to PPD-S than to PPD-B	15	29
Greater to PPD-B than to PPD-S	33	65
Equal induration	1	2
Non-reactors	2	4
Total	51	100

Table 5. This percentage is considerably less than the known percentage of positive reactors to OT or PPD among some 1500 contacts of culturally proved cases of *"typical"* tuberculosis.[2,4,5]

When the 296 contacts were broken down according to age and sex, the number in each group was insufficient to be of any significance. However, it was found that the per cent of men reactors to PPD-B was considerably higher than women for all age groups except from 45-54. There were 117 men and 179 women tested. Of the 117 men, 100 were white and 17 were Negroes. Fifty of the whites and eight of the Negroes were positive. Of the 179 women tested, 161 were white and 18 were Negroes. Thirty-four of the whites and nine of the Negroes were positive.

A group of 140 *non-contacts* of different ages of white and Negro persons have been tested with PPD-S and PPD-B. Of 63 white men tested with PPD-S, 19 had a positive reaction of 6 mm. or more, and of 25 white women tested three were positive. Of the white men tested with PPD-B, 15 were positive while none of the white women had any reaction at all. Of 33 Negro men tested with PPD-S, 16 were positive, and seven of 19 Negro women tested were positive. Eighteen of the 33 Negro men tested with PPD-B were positive, and eight of the 19 Negro women were positive.

Information available at this time shows that the incidence of positive reactors to PPD-B among *"typical"* tuberculous patients, contacts of *"atypical"* patients and *non-contacts* to either form of disease is higher in the Negro than in the white race.

Edwards and Palmer[7] reported 68 per cent of 800 men Navy recruits from the southeastern part of the United States had 6 mm. or more induration to 5 TU of PPD-B. This was in contrast to their findings of only 39 per cent in the mideast, 29 per cent in the northeast and only about 20 per cent[8] in the northwest.

In an unpublished report, Dr. Charles LeMaistre,[9] who recently skin tested 600 men kaolin workers of varying ages in Washington County, Georgia, with the same dose of PPD-B, found that 459 (76.5 per cent) had 5 or more millimeter induration. The exact number who had only 5 mm. induration has not been obtained at this writing.

TABLE 4—REACTION AMONG HOUSEHOLD CONTACTS TO PPD-S AND PPD-B OF ALL AGES, SEX, AND RACE

	Number	Per cent
Non-reactors to both antigens	157	53
Reactors to PPD-S alone		
(a) 6 mm. or over	7	2
(b) Under 6 mm.	6	2
Reactors to PPD-B alone		
(a) 6 mm. or over	59	20
(b) Under 6 mm.	15	5
Reactors to both "S" and "B"		
(a) 6 mm. or over	35	12
(b) Under 6 mm.	6	2
(c) 6 mm. or over to "S" and under 6 to "B"	2	1
(d) 6 mm. or over to "B" and under 6 to "S"	9	3
Total	296	100

TABLE 5—NUMBER AND PER CENT OF CONTACTS WITH 6 MM. OR MORE INDURATION

	Contacts	Per cent
To PPD-B	103	35
To PPD-S	44	15

Discussion

During our early observations these organisms were thought to be saprophytes. After failure to recover *M. tuberculosis* from serial sputum cultures and failure to produce progressive tuberculosis in guinea pigs inoculated with the same specimen of sputa, three of these patients were discharged as being non-tuberculous. Further studies in our laboratory, however, convinced us that these organisms definitely were not saprophytes, as the term is commonly used, in that their growth rate was slower; there was little or no pigment production, and the repeated occurrence of these strains in the sputum and surgically resected specimens of pulmonary tissue indicated the existence of more than a casual relationship.

It became obvious that the incidence of a significant tuberculin reaction among these patients and their contacts was not as high as had been found among culturally proved cases of *"typical"* tuberculosis and their contacts.

It seemed paradoxical not to find a contact case among approximately 500 known contacts, including the spouse, of 151 married or widowed patients.

For some unexplained reason, the ratio of the patients per 100,000 population ranged from 4 to 15 times higher in some of the rural and small town areas than in the urban or more densely populated centers.

It will be recalled that among two different groups of 122 and 336 (458) contacts of *"atypical"* cases, the percentage of reactors to OT or PPD, showing not less than 6 mm. induration, was 29 and 26 per cent respectively. It has been shown that of the 296 contacts tested with PPD-S, only 44, or about 15 per cent, had 6 or more millimeters induration. This 15 per cent is only about half of that seen in the group of 458 tested with OT or PPD. This discrepancy may be due to several factors, such as the difference in numbers tested, the difference in antigens, the possibility that some of the contacts had more exposure to cases of *"typical"* tuberculosis than others, etc.

Since it was found that the per cent of reactors, among contacts, to PPD-S was about equal between men and women and the per cent of reactors to PPD-B among men was twice that of women, there should be a large group of women tested, particularly white women. There is also great need for testing a large group of *non-contacts* of all ages, sex and race with PPD-B, and used as a control.

In addition to focusing our attention on the source of infection and the question of communicability, it must be borne in mind that impaired function of one or both lungs from previous respiratory episodes may play a significant role as a predisposing factor in subsequent development of disease.

Despite the apparent high prevalence of infection in the southeast, the incidence of diesase is extremely low. However, once the disease develops, it poses a much greater treatment problem than does *"typical"* tuberculosis.

There is great need for further epidemiological studies, and other approaches should be made to discover the source of infection, and the mode of transmission. More effective drug therapy is needed to treat this rare but serious disease.

SUMMARY

It has been shown that 158 patients, about one per cent of 15,180 patients, admitted during the past 10 years had demonstrable pulmonary lesions associated with non-photochromogenic mycobacteria in the sputum.

At one time or another, 81 per cent of them had lived on a farm. The ratio of patients per 100,000 population ranged from 4 to 15 times higher in rural and small town areas than in the large, urban centers. The incidence of the disease was higher in the southern than in the northern part of the state.

There was no history or evidence that the spouses of 151 married or widowed patients had ever had tuberculosis.

Pretreatment susceptibility of these organisms to streptomycin showed that 58 patient strains of 81 examined were susceptible, 23 partially resistant and none resistant. The strains of 80 patients were examined for susceptibility to isoniazid and all of whom were resistant.

Response to streptomycin plus PAS, INH plus PAS, or, to all three drugs given simultaneously, was poor. The sputum of about 70 per cent remained positive after many months and even years of treatment.

Only 68 per cent were positive to OT or PPD. Of 51 tested with PPD-S and PPD-B, 54 per cent were positive to S, and 85 per cent were positive to B.

Among 458 household contacts, 27 per cent were positive to OT or PPD. Among 296 household contacts tested with PPD-S and PPD-B, only 15 per cent were positive to S and only 35 per cent were positive to B.

The percentage of positive reactors to B was twice as high in men as in women. The percentage of reactors of all contacts was only 6 per cent greater than that found among a group of 140 *non-contacts*.

The incidence of positive reactors to PPD-B has been found to be greater in the Negro, in all groups tested, than in the white race. However, the incidence of disease in the Negro was found to be only 11.7 per cent of that found in the two races combined. Yet, of the 15,180 patients admitted, 41 per cent were Negroes.

If a 6 mm. or greater induration to PPD-B is accepted as being specific, the incidence of infection is high. However, the incidence of known disease is rare.

From the evidence at hand, we conclude that the source of infection may well be environmental, and that the organisms may be avirulent to man except under certain circumstances or predisposing conditions.

RESUMEN

Se ha mostrado que entre 15,180 enfermos admitidos durante los pasados 10 años, se encontraron 158 con lesiones pulmonares demostrables, asociadas con la presencia de micobacterias no fotocromógenas en el esputo, o sea en el 1 por ciento aproximadamente.

En alguna ocasión en 81 por ciento de ellos habían vivido en una granja, la proporción de enfermos por 100,000 fué de 4 a 15 veces mas alta en los de origen rural o de los pequeños poblados que lo encontrado en los grandes centros urbanos. La incidencia de la enfermedad fué mas alta en el Sur que en el Norte del estado.

No hubo prueba de que el cónyuge de 151 casados o viudos, haya sufrido tuberculosis jamás.

La susceptibilidad de estos gérmenes a la estreptomicina antes del tratamiento, mostró que 58 cepas de enfermos entre las 81 examinadas, eran susceptibles, 23 parcialmente resistentes y ninguno resistente.

Las cepas de 80 enfermos se examinaron respecto de la susceptibilidad a la isoniacida y todas ellas eran resistentes.

La respuesta a la estreptomicina mas PAS, INH mas PAS o a las tres drogas dadas simultáneamente, fué deficiente. El esputo de alrededor de 70 por ciento, permaneció positivo después de muchos meses y aún años de tratamiento.

Sólo 68 por ciento eran positivos a la OT o PPD. De 51 probados con PPD-S y PPD-B 54 por ciento fueron positivos a S y 85 por ciento positivos a B.

Entre los 458 contactos familiares, 27 por ciento fueron positivos a OT o a PPD. Entre los 296 contactos intrafamiliares probados con PPD-S y PPD-B, sólo 15 por ciento fueron positivos a S y sólo 35 por ciento las fueron a B.

El porcentaje de reactores positivos a B, fué doble en los hombres en comparación con las mujeres. El porcentaje de reactores de todos los contactos fué solo ó por ciento mayor que el encontrado en el grupo de 140 no contactos.

La incidencia de los reactores positivos a PPD-B se encontró mayor en negros en todos los grupos estudiados, que en los blancos.

Sin embargo la incidencia de la enfermedad en el negro se encontró que sólo era de 11.7 por ciento de la encontrada en las dos razas combinadas.

Sin embargo, de los 14,180 admitidos el 41 por ciento fueron negros. Si se acepta que una induración de 6 mm. o mas, como respuesta al PPD-B es específica, la incidencia de la infección es alta. Sin embargo la incidencia de enfermedad conocida es rara.

De lo encontrado concluímos que la fuente de la infección bien puede ser ambiental y que los organismos pueden ser avirulentos al hombre excepto bajo ciertas circumstancias o condiciones predisponentes.

RESUMÉ

Sur 15,180 malades hospitalisés durant les dix dernières années, 158, soit environ 1%, eurent des lésions pulmonaires décelables, associées à des mycobactéries non photochromogènes dans l'expectoration.

A un moment ou à un autre, 81% de ces malades ont vécu dans une ferme. Le taux de malades pour 100,000 habitants fut de 4 à 15 fois plus élevé chez la population rurale et les zones de petites villes que dans les grands centres urbains. La fréquence de la maladie fut plus importante dans les régions sud que dans les régions nord de l'état.

Il n'y a pas d'histoire ou de preuve montrant que les épouses des 151 malades ou leurs veuves avaient jamais été atteintes de tuberculose.

La sensibilité de ces germes à la streptomycine avant tout traitement montra que 58 souches sur 81 examinées étaient sensibles, 23 partiellement résistantes, et aucune complètement résistante. Les souches de 80 malades furent examinées au point de vue de la sensibilité à l'isoniazide et toutes se montrèrent résistantes.

Le résultat thérapeutique de la streptomycine associée au P.A.S., de l'isoniazide associé au P.A.S. ou de toutes ces drogues données simultanément se montra médiocre. L'expectoration d'environ 70 malades resta positive après plusieurs mois et même plusieurs années de traitement.

68% seulement furent positifs à la tuberculine brute ou à la tuberculine purifiée. Sur 51 testés avec la P.P.D.-S et la P.P.D.-B, 6.54% furent positifs à la tuberculine S et 85% avec la tuberculine B.

Sur 458 tests pratiqués chez des gens en contact dans leur foyer 27% furent positifs à la tuberculine brute ou à la purifiée. Sur 296 tests pratiqués avec la tuberculine purifiée S et la tuberculine purifiée B, 15% seulement furent positifs à la tuberculine S et 35% seulement à la tuberculine B.

Le pourcentage des réactions positives à la tuberculine B fut deux fois plus élevé chez les hommes que chez les femmes. Le pourcentage des réactions provenant de tous les tests fut seulement plus élevé de 6% par rapport à celui trouvé dans un groupe de 140 personnes n'ayant eu aucun contact avec les tuberculeux.

La fréquence des réactions positives à la tuberculine purifiée B a été trouvée plus élevée chez les Noirs, dans tous les groupes testés, que dans la race blanche. Cependant la fréquence de la maladie chez le Noir ne fut que de 11.7% par rapport à celle constatée dans les deux groupes de races. Notons que, sur 15,180 malades hospitalisés, 41% étaient des Noirs.

Si on admet qu'une induration de 6 mm. au minimum peut être considérée comme spécifique, la fréquence de la maladie à proprement parler est rare.

En possession de faits évidents, l'auteur conclut que la source de l'infection peut parfaitement provenir du milieu environnant, et que d'autre part les bacilles peuvent être avirulents pour l'homme, sauf dans certaines circonstances ou conditions favorisantes.

ZUSAMMENFASSUNG

Es wurde nachgewiesen, daß 158 Patienten d.h. ungefähr 1% von 15,180 während der vergangenen 10 Jahre aufgenommenen Patienten an nachweisbaren Lungenveränderungen in Verbindung mit nicht photochromogenen Mycobakterien im Sputum litten.

Zu irgendeiner Zeit hatten 81% von ihnen auf einem Bauernhof gelebt. Die Verhältniszahl von Patienten auf 100,000 Einwohnern lag zwischen 4 und 15 mal höher im ländlichen Bezirken und Kleinstädten als in großen Städten. Die Krankheitshäufigkeit lag höher im Süden als im Norden des Landes.

E fand sich keine Krankengeschichte oder Anhaltspunkte dafür, daß der Ehepartner von 151 verheirateten oder verwitweten Patenten jemals eine Tuberkulose gehabt hätte.

Die Empfindlichkeit dieser Keime gegen Streptomycin vor Beginn der Behandlung zeigte, daß 58 Patienten-Stämme von 81 geprüften empfindlich waren, 23 teilweise resistent und keiner vollresistent. Die Stämme von 80 Patienten wurden hinsichtlich der INH-Empfindlichkeit geprüft, und sie waren sämtlich resistent.

Die Reaktion auf Streptomycin + PAS, INH + PAS oder auch alle drei gleichzeitig gegebene Medikamente war dürftig. Das Sputum von ungefähr 70% blieb noch positiv viele Monate nach der Behandlung und sogar nach vieljähriger Behandlung.

Nur 68% reagierten auf Alttuberkulin oder PPD positiv. Von den 51 mit PPD-S und PPD-B getesteten Fällen waren 54% positiv auf S und 85 positiv auf B.

Unter 458 Umgebungsfällen im Haushalt reagierten 22% positiv auf Alttuberkulin oder PPD. Von 296 Umgebungsfällen im Haushalt, die mit PPD-S und PPD-B getestet wurden, waren nur 15% positiv auf S und nur 35% positiv auf B.

Der Prozentsatz positiver Reaktoren auf B war bei Männern doppelt so hoch wie bei Frauen. Der Prozentsatz von Reaktoren unter allen Umgebungsfällen lag nur um 6% häher als in einer Gruppe von 140 nicht Umgebungsfällen.

Das Auftreten positiver Reaktionen auf PPD war in allen getesteten Gruppen häufiger bei Negern als bei angehörigen der weißen Rasse. Jedoch betrug die Krankheitshäufigkeit bei Negern nur 11.7% der-jenigen, die bei beiden Rassen kombiniert gefunden wurde. Gleichwohl befanden sich unter den 15,180 auggenommenen Kranken 41% Neger.

Sofern mna von einer Induration von 6 mm Durchmesser oder mehr annimmt, daß sie spezifisch sei, so ist die Häufigkeit der Infektion beträchlich. Jedoch ist die Häufigkeit bekannter Er-Krankungen gering.

Aus den auf der Hand liegenden Befunden schliessen wir, daß die Keime für den Menschen avirolent sein können, außer unter bestimmten Bedingungen oder prädisponierenden Umständen.

Complete reference list will appear in the reprints.

A Transistor Electronically Controlled Respirator*

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The use of mechanical devices to aid respiration has become an important part in the therapy of bulbar poliomyelitis, pulmonary emphysema, asthma, and other entities in which there is respiratory failure.

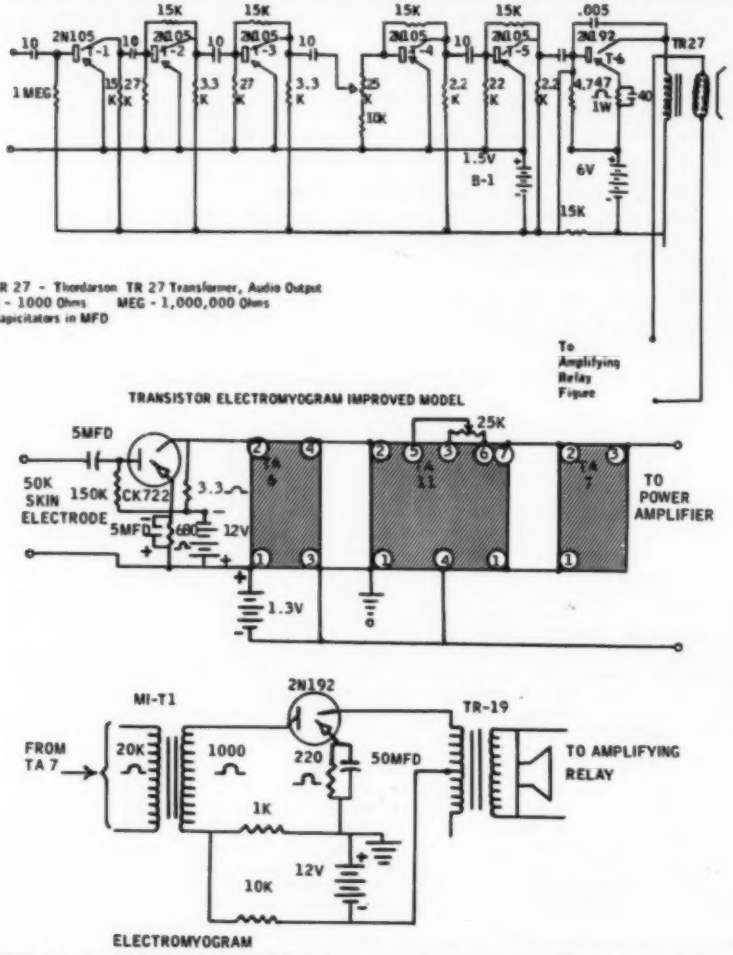

FIGURE 1A (upper): Transistor Electromyogram Improved Model. Improved electromyogram designed by Radioisotope Service, V. A. Hospital, Hines, Illinois. Dr. Irvin Kaplan is Chief of the Service. FIGURE 1B (lower): Electromyogram. Early Transistor Electromyogram. TA6=Centralab TA6—1 Transistor input amplifier; TA11=Centralab TA11—4 Transistor amplifier; TA7=Centralab TA7—1 Transistor output amplifier. Lead numbers as marked on case. MI-T1=Thordarson Miniature interstage transformer 20,000 ohm primary, 1,000 ohm secondary; TR-19=Thordarson TR-19 Transformer, primary 400 ohm, secondary 11 ohm.

*From the Veterans Administration Hospital and Baylor University College of Medicine.

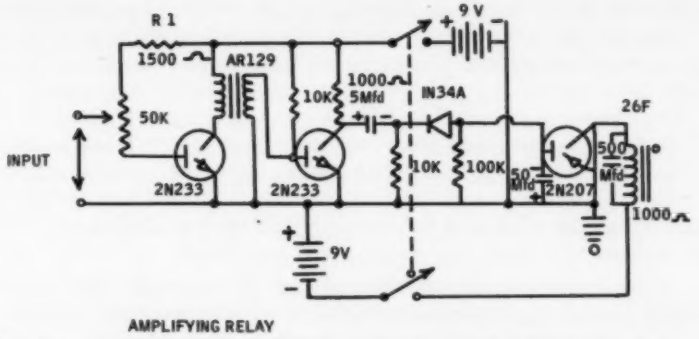

FIGURE 2: Amplifying Relay. AR129=Argonne Input Transistor Transformer, primary 50,000, secondary 1,000; 26F=Sigma Relay 1,000 ohm, 26F-S.

The control of these devices usually depends upon pre-set variations of rate and pressure of the instrument or upon the patient's ability to produce sufficient pressures to control the apparatus. The major problems inherent in these systems are: (1) the operator must be able to estimate accurately the indicated respiratory rate and pressures which provide optimal blood gas concentrations, or (2) the patient must be able to exert sufficient pressures to cycle the apparatus in the case of patient-controlled respiratory assisting devices.

In our experience, these control systems may not be able to properly ventilate the extremely debilitated patient whether it be from nearly complete respiratory paralysis in poliomyelitis, or from far-advanced pulmonary emphysema. In patients where primary respiratory center failure is not the cause of decreased respiration, this center may remain as an automatic control mechanism whereby blood gases and blood pH may be kept within the normal range if sufficient assistance to the normal efforts of respiration are given.

The first device we evaluated which employed the respiratory center as a driving force was described by Batson, Montgomery, *et al.* in 1957.[1] This

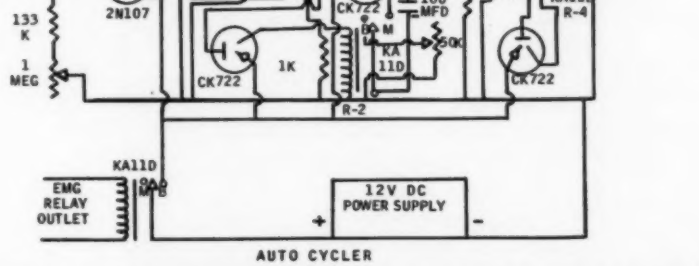

FIGURE 3: Auto Cycler. KAIID=Potter and Brumfield 6V D.C. Relay; BK-7-B=Allen D. Cardwell Relay; Sigma 26F=Sigma 1,000 ohm relay, 26F-S; TR98=Lafayette Transistor Interstage Transformer TR98, primary 10,000 ohms, secondary 2,000 ohms.

vacuum tube device used the principle of the electromyogram which in turn could be used to drive an electrically powered respirator. An automatic cycling mechanism was included which would continue to ventilate the patient should the respiratory rate fall below a pre-determined level. This device is reported to have worked satisfactorily and a similar device designed around this report was constructed in our laboratory and found to cycle successfully. In our hands, however, certain difficulties were encountered: the sensitivity of the device limited the usefulness of the apparatus, interference by 60-cycle sources was found and electric shock was possible when the patient was grounded.

As a consequence of our difficulties with the vacuum tube circuit, a transistor circuit was designed. For ease of construction, design, and testing, our apparatus has been placed in individual boxes.

The first unit, as shown in Figure 1B consists of a transistorized electromyogram. A more sensitive circuit designed by the radioisotopes unit, Veterans Administration Hospital, Hines, Illinois was eventually adapted as the most suitable electromyogram (Figure 1A).

It was found that needle plunge electrodes as used in most electromyographic devices, were not practical because of severe muscular pain which developed over prolonged periods of use. Skin electrodes were therefore employed, with skin resistances at approximately 50,000 ohms. The pre-amplifier in the electromyogram shown in 1B provides compatibility with this skin resistance. The additional amplifying stages provide increased sensitivity and allow for better filtering of extraneous AC currents.

A sensitive relay unit is shown in Figure 2. Its connection to the electromyogram is such as to permit auditory monitoring while the respirator is in operation without interference from the relay circuit. The large capacitator across the relay is necessary to avoid relay chatter from the approximately 400 cycle per second current obtained from the electromyogram. The output of this relay may be coupled directly to a solenoid which controls the valve of an intermittent positive pressure breathing valve. Alternately, the output may be connected to a heavy wattage relay and then employed to run a cuirasse or greatly modified Emerson respirator directly.

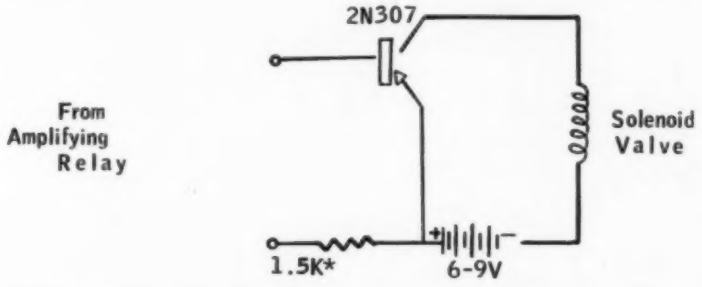

FIGURE 4: Final Solenoid Driving Stage. Solenoid is any 6-9V solenoid. We employed one made for juke boxes.

The automatic cycler (Figure 3) is a combination of an electronic metronome and a delayed action relay. This can be set by variable resistance so that cycling is obtained between a rate of 5 and 40 per minute. The variable resistance in the delay allows for a selection of the relative duration of expiration and inspiration. Electromyographic impulses obtained during the patient's voluntary respirations short circuit the base capacitator on the electric metronome, preventing its cycle from being initiated. Thus, if the patient breathes at a rate faster than pre-set upon the automatic cycler, no cycling will be obtained. If, however, the patient should cease breathing or slow breathing to less than the pre-determined rate, then the automatic cycler immediately controls respiration.

Driving a respirator is done either by means of an air solenoid or by means of a solenoid to trip the respirator valve (Figure 5).

The instrument as constructed above and connected by shielded cable, is readily portable from room to room and from bed to bed. The transistor electromyogram may be used for monitoring muscle potentials. One can thus readily select muscle groups for proper electrode placement. Interference is minimal, permitting the use of suction devices and other necessary equipment within the immediate area of the patient. As the instrument produces no sparks, it may be used in the presence of oxygen. Heat production is below detectable levels. Battery life is extremely long

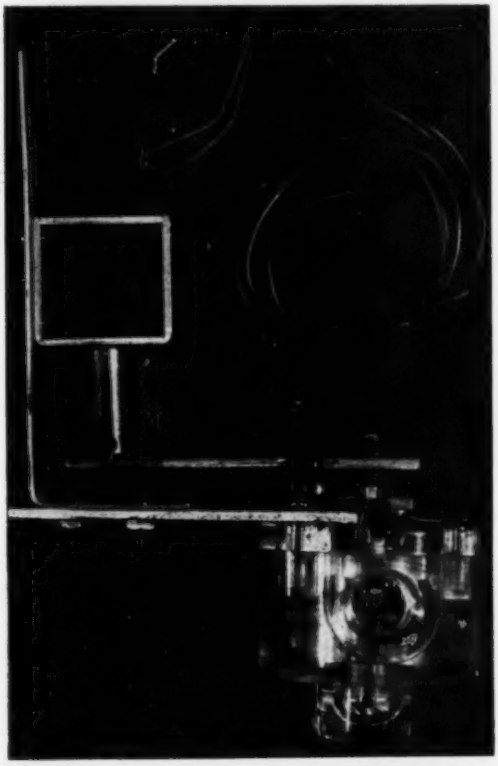

FIGURE 5: Solenoid attached to Halliburton valve.

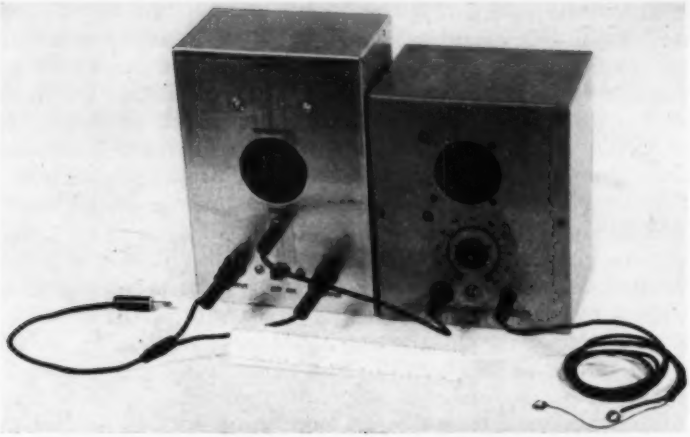

FIGURE 6: The "Respirator" in its presently constructed state.

so that no attempt has been made to provide an additional power supply except in the final driving stages. The cost of construction of this unit is from $75.00 to $100.00. As there is marked variation in the characteristics of individual transistors, it is necessary that pilot devices be built upon an individual basis. An instrument built with commercial parts will thus require alterations in resistances, impedances, filters, etc., for maximal results.

With refinements in design, it is easily feasible for this device to be built entirely into a metal cabinet, 3x5x6 inches. At the present time two 3x5x4 inch cabinets are employed, but they are not considered necessary. The "Respirator" in its presently constructed state is seen in Figure 6.

Provisions are made for the actual breathing device to run either on the make or break of the output relay. Such construction is necessary as some patients may have maximal potentials occurring in certain muscles during inspiration rather than expiration. At times intercostal muscles and diaphragm, for instance, are practically non-functioning, and cervical muscles have to be employed. Most cervical accessory muscles operate maximally during inspiration and are inactive during expiration. In other patients intercostal muscle potentials will be found maximal and occur on expiration.[2-5] Movements of the patient during the operation have insignificant effect.

SUMMARY

The transistor electronically controlled respirator offers potentialities for aiding respiration in patients with insufficient respiratory force to trip the positive pressure respirators, and in patients with respiratory muscle paralysis. Increased sensitivity of pressure operated respirators often leads to chattering of the respirator due to alterations of air flow and pressure secondary to retained secretions in the respiratory tract. Such an effect is obviated with the present system. The use of the patient's own respiratory center to regulate breathing allows more adequate respiratory assistance. The dangers of hypoventilation are reduced as the patient's own respiratory center is the major controlling center. The automatic cycler prevents or diminishes the dangers arising from complete respiratory center failure. An alarm monitor system is possible even if the device is not used to control respirations.

RESUMEN

El respirator electrónico controlado por transitores ofrece posibilidades para ayudar a la respiración de los enfermos con insuficiencia respiratoria para recibir la presión positiva de los respiradores y en los enfermos con parálisis de los músculos respiratorios.

La sensibilidad aumentada de los respiradores a menudo conduce a un funcionamiento trémulo del respirador debido a las alteraciones de corriente de aire y a presión consecutiva a secreciones retenidas en las vías respiratorias. Tal efecto se evita con el sistema actual. El uso del mismo centro respiratorio del enfermo para regular la respiración permite mejor ayuda respiratoria. Los peligros de la hipoventilación se reducen puesto que el propio centro respiratorio del enfermo es el mejor control. El ciclaje automático evita o disminuye los peligros emanados de la falla completa del centro respiratorio. Un sistema de monitor de alarma es posible que actúe aunque ese monitor no se use para controlar las respiraciones.

RESUMÉ

Le respirateur à transistor contrôlé électroniquement offre des possibilités d'aider la respiration chez les malades dont la puissance respiratoire est insuffisante pour utiliser les respirateurs à pression positive et chez les malades atteints de paralysie des muscles respiratoires. Une augmentation de la sensibilité des respirateurs à pression conduit souvent au bruissement du respirateur, imputable aux altérations du bébit de l'air et à la pression qu'entrainent les sécrétions retenues dans l'arbre respiratoire. Le système actuel fait obstacle à un tel effet. L'utilisation du propre centre respiratoire du malade pour régulariser la respiration permet une assistance respiratoire plus convenable. Les dangers de l'hypoventilation sont réduits puisque le propre centre respiratoire du malade est le meilleur centre de contrôle. L'appareil automatique évite ou diminue les dangers provenant d'une défaillance totale du centre respiratoire. Un système d'alarme est possible, même s'il n'y a pas de contrôle graphique de la respiration.

ZUSAMMENFASSUNG

Die elektronisch durch Transistoren gesteuerten Respiratoren bieten die Möglichkeit, die Atmung zu verbessern bei Kranken, deren Atemtätigkeit so unzulänglich ist, daß sie die positiven Druck-Respiratoren fehlerhaft bedienen und bei Kranken mit Lähmungen der Atemmuskulatur. Erhöhte Empfindlichkeit von mit Druck gesteuerter Respiratoren führt oft dazu, daß der Respirator klappert infolge Störungen in der Luftzirkulation und im Druck in Zusammenhang mit Sekretverhaltungen im Respirationstrakt. Ein solcher Effekt wird mit dem dargestellten System vermieden. Der Einsatz des Atemzentrums des Kranken selbst zur Steuerung der Atmung ermöglicht eine mehr angepaßte Unterstützung der Atmung. Die Gefahren einer Hyperventilation werden geringer, weil das Atemzentrum des Kranken selbst das wesentliche Kontrollzentrum ist. Das automatische Steuergerät verhütet oder verringert die Gefahren, die von einem kompletten Versagen des Atemzentrums ihren Ausgang nehmen. Ein Alarm- und Warnsystem ist möglich selbst dann, wenn die Vorrichtung nicht gebraucht wird, um die Atmung zu kontrollieren.

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The Effect of Respiratory Tract Obstruction Upon the Ventilatory Response to Inhaled Carbon Dioxide in Normal Subjects[1,2]

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The factors responsible for the depressed ventilatory response to inhaled carbon dioxide in patients with obstructive pulmonary emphysema and hypercapnia remain a subject for intensive study. Two concepts have been advanced to explain this abnormal response. The first is respiratory center depression;[3-4] the second is an increase in the work of breathing due to abnormal ventilatory mechanics.[5-6] The purpose of the present study is to delineate the ventilatory response to inhaled carbon dioxide in normal subjects under control conditions and during the interposition of varied grades of respiratory tract obstruction.

Subjects

Fourteen normal subjects were studied; all but one were men. The vital statistics and control and experimental maximum breathing capac-

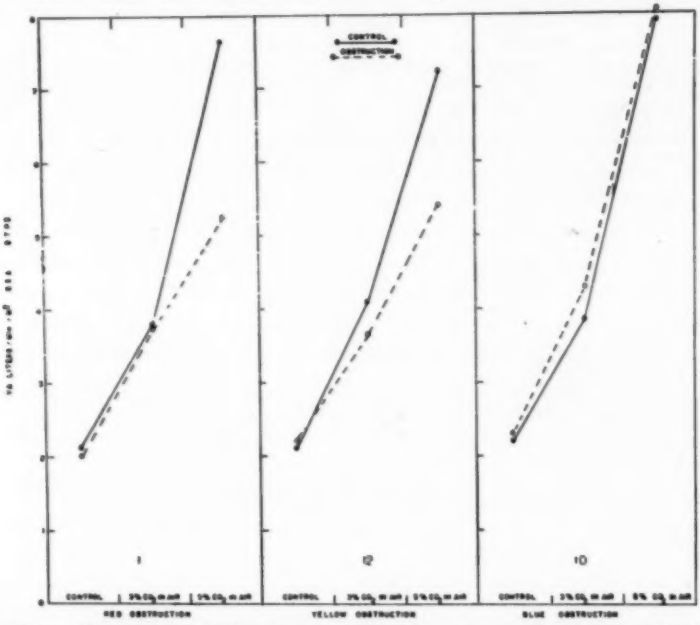

FIGURE 1: Alveolar ventilation during inhalation of compressed air, and 3 and 5 per cent CO_2 in air during control studies and three grades of respiratory tract obstruction.

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[2]Supported in part by a grant from the Heart Association of Greater Miami, and from the National Heart Institute (H-4249).

ities are listed in Table 1. The entire group was gainfully employed at the time of study.

Methods

All patients were investigated in the basal postabsorptive state without prior sedation. Control measurements of minute ventilation, arterial oxygen saturation, arterial carbon dioxide tension, arterial blood pH, oxygen consumption, respiratory quotient and respiratory rate were made while breathing compressed air, 3 per cent CO_2 in air and 5 per cent CO_2 in air. One of three grades of respiratory tract obstruction was then inserted into the mouthpiece outlet of a Collins double Jap valve respiratory valve so as to provide inspiratory as well as expiratory obstruction. The above measurements were then repeated during respiratory tract obstruction. In nine subjects studies were made at two grades of respiratory tract obstruction.

The three grades of obstruction were provided by No. 1 rubber stoppers. Each stopper was 27 mm. in length. The top surface measured 14.5 mm. in diameter; the under surface was 19.5 mm. in diameter. Three sized holes were drilled in these stoppers. The smallest was 4.5 mm. in diameter —the red obstruction.* The largest opening measured 7.3 mm. in diam-

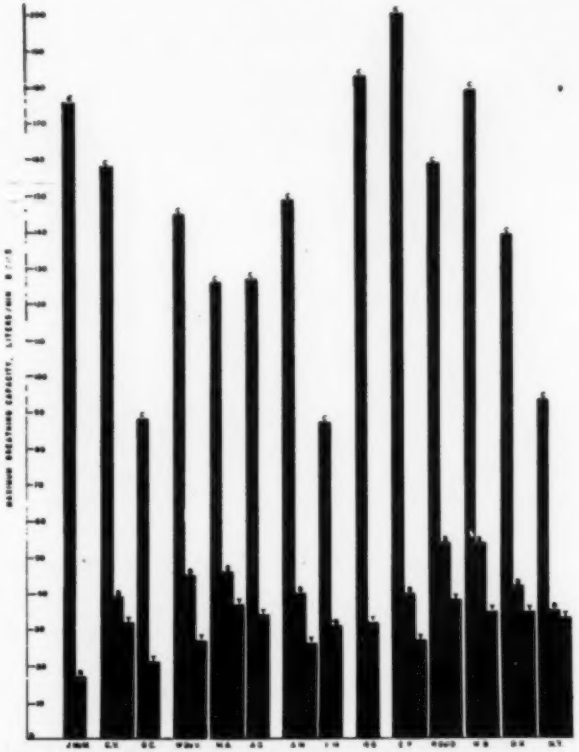

FIGURE 2: Maximum breathing capacities in 14 subjects under control conditions and three grades of respiratory tract obstruction.

TABLE 1—VITAL STATISTICS AND MAXIMUM BREATHING CAPACITY IN 14 NORMAL SUBJECTS

Subject	Age (yrs.)	Sex	Ht. (inches)	Wt. (lbs.)	B.S.A. ($M.^2$)	Obstruction	M.B.C.-Predicted (L./Min.)	M.B.C.-Control (L./Min.)	M.B.C.-Control per cent Pred.	M.B.C.-Obstruction Red (L./Min.)	Red per cent Pred.	Yellow (L./Min.)	Yellow per cent Pred.	Blue (L./Min.)	Blue per cent Pred.
J.McM.	32	M	69	148.5	1.81	Red	126	176	140	17	13				
C.V.	31	M	66.3	204	2.02	Yellow-Blue	142	158	111			32	23	39	27
G.C.	24	M	63	104.5	1.46	Yellow	108	88	81			21	19		
W.DeV.	26	M	69.5	172	1.95	Yellow-Blue	142	145	102			27	19	45	32
M.A.	26	M	73.5	148.5	1.90	Yellow-Blue	139	126	96			37	27	46	32
A.G.	24	M	63	123	1.58	Yellow	117	127	109			34	29		
A.M.	27	M	65	150.5	1.75	Yellow-Blue	125	149	119			26	17	40	32
E.M.	34	F	62.5	125	1.58	Blue	103	87	84					31	30
R.G.	30	M	68.8	201	2.07	Yellow	139	183	132			32	23		
E.F.	30	M	71.8	229	2.25	Yellow-Blue	156	200	130			27	17	40	25
R.Del P.	37	M	66.5	163.5	1.85	Yellow-Blue	125	159	127			38	30	54	43
W.B.	39	M	69.5	184	2.05	Yellow-Blue	135	179	133			35	26	54	40
D.K.	21	M	70	135	1.77	Yellow-Blue	136	139	102			34	25	42	31
H.T.	37	M	61.5	114	1.50	Yellow-Blue	101	93	93			33	33	35	35

eter—the blue obstruction.* The intermediate grade of obstruction contained an opening of 6 mm. in diameter—the yellow obstruction.*

All gas mixtures were inhaled for at least 15 minutes (employing an open circuit) before the collection of either blood or gas samples was begun. This time schedule permitted attainment and maintenance of a "steady rate" of respiration and circulation[7] in most, but not all, subjects.

Expired gas samples were collected in a 120 L. Tissot spirometer and analyzed in duplicate for oxygen and carbon dioxide on a micro-Scholander apparatus, thus permitting calculation of oxygen consumption, carbon dioxide production, respiratory quotient and minute ventilation. Arterial blood samples were obtained via an indwelling Cournand needle and analyzed for oxygen and carbon dioxide content and for oxygen capacity on a Van Slyke apparatus. Arterial blood pH was determined at a constant temperature of 37°C, employing a Cambridge Research Model pH meter. The line charts of Van Slyke and Sendroy were utilized to calculate arterial blood carbon dioxide tension. Alveolar ventilation

*The rubber stoppers were painted different colors.

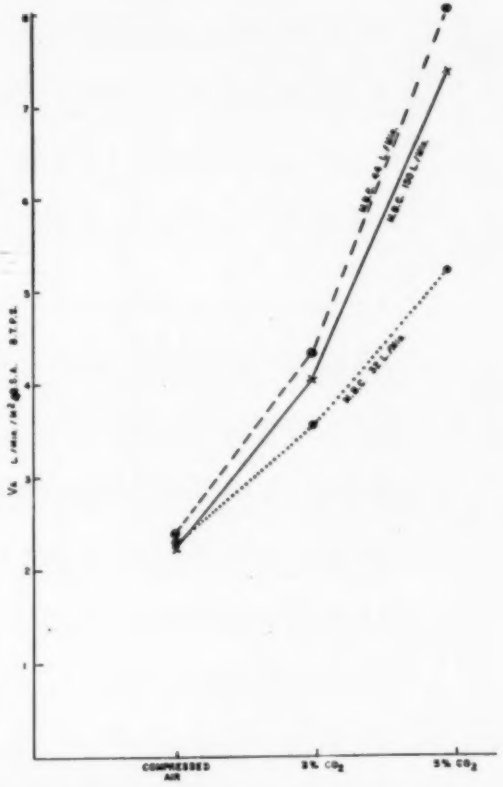

FIGURE 3: Alveolar ventilation during inhalation of compressed air and 3 and 5 per cent CO_2 in air in nine subjects at three different levels of maximum breathing capacities. The limited effect of a decrease in maximum breathing capacity from 150 to 44L./min. is readily seen.

TABLE 2—VENTILATION AND GAS EXCHANGE DATA BEFORE AND DURING RESPIRATORY TRACT OBSTRUCTION

Subject		Compressed Air					3 per cent CO_2 — 21 per cent O_2						5 per cent CO_2 — 21 per cent O_2						
		$\dot{V}O_2$ (ml./Min./M.²)	R	$\dot{V}E^{**}$ (L./Min./M.²)	$\dot{V}A$ (L./Min./M.²)	f/Min.	$\dot{V}O_2$ (ml./Min./M.²)	R	$\dot{V}E^{**}$ (L./Min./M.²)	$\dot{V}E$ per cent I vs. Ca*	$\dot{V}A$ (L./Min./M.²)	$\dot{V}A$ per cent I vs. CA	f/Min.	$\dot{V}O_2$ (ml./Min./M.²)	R	$\dot{V}E^{**}$ (L./Min./M.²)	$\dot{V}E$ per cent I vs. CA	$\dot{V}A$ (L./Min./M.²)	$\dot{V}A$ per cent I vs. CA	f/Min.
A. Red and Blue Obstruction																			
J.McM.	Control	133	.76	4.39	2.14	11.2	129	.73	6.41	46	3.81	78	11	152	.65	14.2	223	7.69	260	17
	Red	129	.79	4.02	2.04	8	144	.74	5.45	36	3.81	87	7.5	198	.58	7.13	128	5.28	160	9.4
C.V.	Control	119	.73	4.05	1.79	11.2	116	.73	6.47	60	3.25	82	12.8	138	.64	13.9	243	9.48	429	22.3
	Blue	127	.79	4.72	2.05	9.5	122	.74	5.36	14	3.32	61	11.2	121	.74	9.65	104	6.15	200	16
W.DeV.	Control	139	.64	4.19	1.86	20.7	164	.73	8.98	115	4.45	140	22	137	.88	14.5	247	8.29	345	24
	Blue	130	.85	4.27	2.40	14.5	147	.83	7.16	68	4.56	90	16	191	.77	14.3	234	9.28	283	21
M.A.	Control	167	.78	4.75	2.65	14.2	165	.80	8.00	68	4.91	86	17.1	176	.97	18.7	294	10.1	282	19.3
	Blue	173	.84	4.98	3.01	16	178	.92	9.90	99	6.91	130	16	221	.78	16.9	240	13.0	333	20.6
A.M.	Control	121	.79	4.96	1.99	14	115	.83	7.55	52	3.61	81	15.5	124	.73	10.8	117	5.49	175	17
	Blue	122	.82	4.80	1.79	15.5	133	.71	7.27	52	3.61	101	12.8	124	.76	9.53	99	5.39	200	12
E.M.	Control	117	.79	5.27	2.19	15.3	110	.79	6.94	32	4.16	90	16.8	128	.65	14.2	170	11.0	400	20
	Blue	110	.90	5.01	2.25	13.5	121	.72	7.25	45	4.49	100	13.8	128	.68	11.8	136	7.14	217	18.7
E.F.	Control	124	.74	3.32	1.74	6.5	127	.76	5.83	76	3.32	91	12	127	.85	15.1	354	8.34	378	13
	Blue	118	.71	3.46	1.66	8	119	.77	6.27	81	3.40	105	8	136	.80	11.7	238	8.09	385	9
R.Del P.	Control	148	.91	5.58	2.91	6.5	146	.67	7.43	33	3.41	17	10	151	.68	9.37	68	6.00	106	11.5
	Blue	161	.86	5.39	3.09	5	148	.71	8.27	54	3.93	27	5.5	153	.77	9.94	86	7.73	151	13
W.B.	Control	140	.74	5.07	2.44	17	151	.72	9.10	80	4.64	82	21.5	152	.75	16.8	231	8.36	242	27.3
	Blue	134	.82	4.69	2.26	19	162	.80	10.12	116	5.40	140	24	181	.74	14.1	201	9.43	318	25
D.K.	Control	144	.69	5.16	2.63	14.8	140	.66	6.63	28	3.36	28	16.2	156	.67	9.81	90	6.06	127	16
	Blue	136	1.05	5.51	3.32	14	138	.73	5.98	27	3.41	3	12.2	150	.76	8.78	59	6.23	88	12
H.T.	Control	125	.82	5.97	2.06	20.5	133	.73	9.37	57	3.71	80	21.2	163	.60	19.8	231	6.13	198	23.3
	Blue	126	.83	6.02	1.99	19	146	.75	9.19	53	4.12	107	17.8	171	.77	15.5	158	8.00	300	18.7
Average	Control	134	.763	4.83	2.23	14.1	137	.742	7.63	60	3.88	78	16.5	145	.742	14.3	205	7.93	268	19.4
	Blue	134	.847	4.89	2.38	13.4	141	.768	7.68	61	4.32	86	13.7	158	.757	12.2	168	8.04	248	16.6

TABLE 2—(CONTINUED)

B. Yellow Obstruction

C.V.	Control	123	.82	4.26	1.95	10.5	124	.68	7.38	73	3.86	98	12.5	147	.66	12.8	201	6.28	222	19.8
	Yellow	127	1.01	4.12	2.82	10	133	.68	4.62	12	3.29	17	12	154	.62	7.06	71	4.88	73	12
G.C.	Control	129	.79	4.51	1.83	21.3	129	.69	7.29	62	3.44	88	23.5	144	.61	12.1	168	5.89	222	29.8
	Yellow	114	.92	4.99	2.40	18	125	.74	6.51	30	3.73	55	18.5	138	.65	8.96	80	6.54	172	18
W.DeV.	Control	129	.60	5.63	1.58	13.5	143	.68	7.72	37	3.77	139	22	132	.76	17.3	209	6.50	312	28
	Yellow	118	.72	4.16	1.70	15	141	.72	5.31	28	2.75	62	14.7	167	.58	7.94	91	3.92	131	17
M.A.	Control	147	.86	4.52	2.57	15	155	.85	8.08	79	5.10	98	15	164	.76	15.1	234	8.88	245	17
	Yellow	141	.80	3.75	2.15	13.3	173	.77	7.44	98	4.44	107	16	255	.64	10.6	183	6.15	186	20
A.G.	Control	128	.84	4.94	2.07	15.5	130	.87	7.11	44	4.54	119	17.5	131	.83	14.4	191	10.3	399	22.3
	Yellow	127	.82	5.47	2.14	11	127	.85	7.35	34	4.20	96	15	144	.72	9.91	81	6.76	216	17
A.M.	Control	116	.76	4.14	1.77	13.8	119	.76	6.20	50	3.63	105	15.5	122	.70	12.6	205	7.10	301	14
	Yellow	129	.79	5.05	2.01	8.3	130	.70	5.49	9	3.46	72	7.5	148	.66	7.85	55	3.61	80	8
R.G.	Control	121	.71	4.13	1.84	12	124	.68	6.26	52	3.37	83	16.5	138	.63	12.4	200	6.15	234	17
	Yellow	121	.76	4.25	1.94	7	132	.73	6.82	61	3.95	104	8.3	157	.61	8.77	107	5.15	165	16.3
E.F.	Control	132	.70	3.52	1.92	7	133	.73	6.20	76	3.91	104	10	134	.67	13.3	277	5.48	185	12.7
	Yellow	126	.69	3.40	1.87	4	134	.71	6.31	85	3.46	85	5	143	.68	8.67	155	5.49	194	7.5
R.Del P.	Control	128	.87	4.19	2.52	10	151	.78	6.41	53	4.23	68	6.5	152	.72	9.60	129	5.65	124	10
	Yellow	132	.94	4.64	2.76	4.5	158	.71	6.92	49	3.88	41	5.5	147	.73	7.45	60	5.22	89	10
W.B.	Control	120	.94	5.14	2.53	19	150	.80	9.67	88	5.43	115	22.5	180	.65	16.7	225	7.79	208	28
	Yellow	137	.79	5.23	2.37	25	162	.77	7.88	51	4.02	69	26.5	259	.63	11.4	118	6.45	172	30
D.K.	Control	142	.83	5.24	2.64	16.5	149	.74	6.75	29	3.71	41	18.3	158	.82	10.5	101	6.09	131	16
	Yellow	134	.90	4.97	2.64	13.8	124	.74	5.17	4	3.08	17	13	181	.72	10.2	105	6.23	136	19.3
H.T.	Control	139	.85	6.57	2.28	21.5	131	.86	10.4	58	4.21	85	22	152	.84	19.9	203	11.1	387	22.7
	Yellow	103	.89	4.81	1.86	18.5	139	.78	9.83	104	3.51	89	18.5	181	.66	14.2	195	4.87	162	23.5
Average	Control	130	.798	4.73	2.13	14.6	137	.760	7.46	58	4.10	95	16.8	146	.721	13.9	195	7.27	248	19.3
	Yellow	126	.858	4.57	2.22	12.4	140	.742	6.64	47	3.65	68	13.4	173	.658	9.41	108	5.44	148	16.6

**See text for discussion of errors in V_E

*I vs. CA=Increase vs. Compressed Air

was calculated from the minute volume, arterial carbon dioxide tension, respiratory rate and expired gas carbon dioxide tension by the Bohr equation. Maximum breathing capacities were performed on a 13L Collins spirometer from which all valves and the CO_2 absorber had been removed.

Results

The ventilatory and gas exchange data before and during respiratory tract obstruction in both inspiration and expiration are illustrated in Table 2 for the three grades of obstruction employed.

After the study was completed, it was found that the Jap valves provided so minimal a resistance to flow that some of the cylinder gas bypassed the patient on inspiration, opened the expiratory valve and passed directly into the Tissot spirometer. This factor resulted in an apparent but false elevation of the patients' dead space. As a result, the ratios of dead space to tidal volumes (which can be calculated from Table 2) are elevated. This error falsely increases both minute ventilation and dead space ventilation, but of course has no effect upon the calculated alveolar ventilation. The minute ventilations are thus some 15 to 25 per cent too high in this study. Analysis of the effect of respiratory tract obstruction

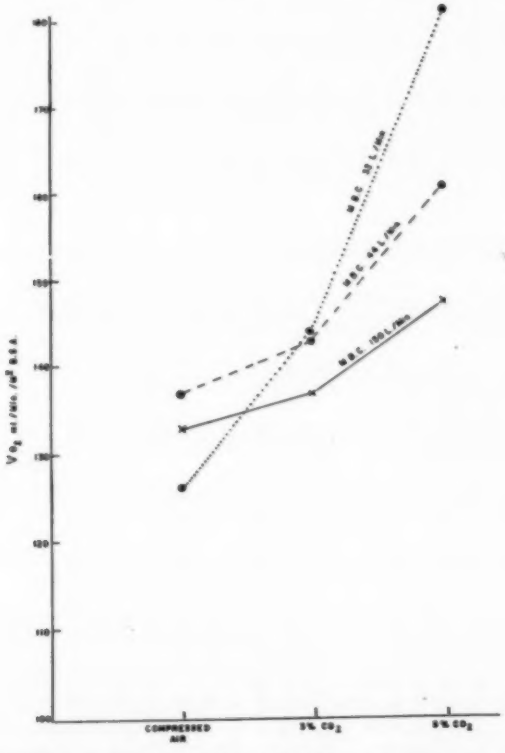

FIGURE 4: Oxygen consumption during inhalation of compressed air and 3 and 5 per cent CO_2 in air in the same nine subjects at three different levels of respiratory tract obstruction.

TABLE 3—ARTERIAL BLOOD GAS DATA BEFORE AND DURING RESPIRATORY TRACT OBSTRUCTION

Subject		Compressed Air			3 per cent CO_2 - 21 per cent O_2			5 per cent CO_2 - 21 per cent O_2		
		SaO_2 per cent	$PaCO_2$ (mm.Hg.)	pH	SaO_2 per cent	$PaCO_2$ (mm.Hg.)	pH	SaO_2 per cent	$PaCO_2$ (mm.Hg.)	pH
A. Red and Blue Obstruction										
J.McM.	Control	93	41	7.39	96	45	7.36	97	48	7.34
	Red	94	42	7.38	97	48	7.34	99	57	7.28
C.V.	Control	95	42	7.40	98	46	7.37	98	49	7.35
	Blue	96	43	7.39	97	47	7.36	100	51	7.34
W.DeV.	Control	95	42	7.39	99	46	7.36	99	50	7.34
	Blue	97	40	7.41	99	46	7.37	99	51	7.33
M.A.	Control	99	43	7.36	99	46	7.35	100	50	7.33
	Blue	99	42	7.38	98	43	7.37	97	47	7.33
A.M.	Control	97	42	7.39	99	45	7.36	100	50	7.33
	Blue	97	43	7.38	97	45	7.36	99	51	7.33
E.M.	Control	94	37	7.40	97	40	7.37	98	45	7.34
	Blue	98	38	7.40	99	42	7.37	98	49	2.32
E.F.	Control	97	44	7.40	99	48	7.37	99	47	7.37
	Blue	95	44	7.40	97	46	7.38	98	47	7.38
R.Del P.	Control	99	40	7.40	99	47	7.36	100	50	7.34
	Blue	95	39	7.42	96	47	7.36	98	49	7.34
W.B.	Control	96	37	7.42	100	43	7.37	99	48	7.33
	Blue	98	42	7.37	98	45	7.35	97	51	7.31
D.K.	Control	99	33	7.43	98	46	7.37	100	51	7.33
	Blue	98	38	7.43	97	48	7.36	98	52	7.33
H.T.	Control	93	43	7.36	97	45	7.35	100	51	7.31
	Blue	94	45	7.35	98	46	7.35	98	51	7.30
Average	Control	96.4	40	7.40	98.5	45	7.36	99.3	49	7.34
	Blue	96.7	41	7.39	97.6	46	7.36	98.2	50	7.33
B. Yellow Obstruction										
C.V.	Control	96	45	7.39	97	49	7.36	98	50	7.35
	Yellow	99	40	7.43	98	49	7.36	100	54	7.33
G.C.	Control	96	43	7.38	98	46	7.35	100	50	7.33
	Yellow	97	38	7.41	98	45	7.36	97	49	7.33
W.DeV.	Control	94	43	7.38	98	46	7.36	99	52	7.31
	Yellow	96	44	7.36	97	51	7.33	99	56	7.30
M.A.	Control	95	44	7.36	98	46	7.35	100	51	7.32
	Yellow	95	46	7.36	99	51	7.34	98	62	7.25
A.G.	Control	96	43	7.39	97	45	7.37	99	48	7.33
	Yellow	98	43	7.38	97	46	7.36	97	52	7.33
A.M.	Control	98	44	7.39	99	46	7.36	98	50	7.34
	Yellow	96	44	7.38	97	47	7.35	100	55	7.30
R.G.	Control	95	41	7.39	97	44	7.36	99	48	7.33
	Yellow	98	41	7.38	97	44	7.36	97	52	7.31
E.F.	Control	96	42	7.40	100	46	7.36	100	50	7.33
	Yellow	94	41	7.40	98	46	7.36	98	51	7.33
R.Del P.	Control	96	39	7.42	99	46	7.35	98	52	7.32
	Yellow	96	39	7.41	97	47	7.36	99	53	7.32
W.B.	Control	95	39	7.40	98	43	7.36	99	49	7.32
	Yellow	95	40	7.39	100	48	7.32	98	58	7.25
D.K.	Control	97	39	7.42	96	48	7.36	98	54	7.32
	Yellow	99	40	7.42	98	48	7.35	98	54	7.30
H.T.	Control	97	42	7.36	98	46	7.34	99	52	7.29
	Yellow	98	43	7.36	99	48	7.33	97	58	7.25
Average	Control	95.9	42	7.39	97.9	46	7.36	98.9	51	7.32
	Yellow	96.7	42	7.39	97.9	48	7.35	98.2	55	7.30

on the response to inhaled CO_2 has therefore been limited to alveolar ventilation; minute ventilation changes and related data were not statistically analyzed because of this 15 to 25 per cent error.

Ten subjects were studied before and during interposition of the blue obstruction—7.3 mm. diameter. This degree of obstruction produced no significant change ($P>0.05$) in oxygen consumption, respiratory quotient, respiratory rate or alveolar ventilation during inhalation of compressed air. During inhalation of 3 and 5 per cent CO_2, no significant change ($P>0.1$) resulted in oxygen consumption, respiratory quotient and alveolar ventilation. A significant fall did result however in respiratory rate during obstructed breathing, $P<0.01$.

Twelve subjects were studied before and during the yellow obstruction —6 mm. diameter. This degree of obstruction produced no significant change ($P>0.05$) in the parameters measured in Table 2 during inhalation of compressed air. During inhalation of 3 per cent CO_2, oxygen consumption remained unchanged ($P>0.3$) as did the respiratory quotient ($P>0.4$); the alterations in alveolar ventilation and the per cent increment in alveolar ventilation were of some significance, $0.02>P>0.01$; the decrease in respiratory rate was significant, $P<0.01$. During inhalation of 5 per cent CO_2 on the other hand, the increase in oxygen consumption after interposition of respiratory tract obstruction was probably significant, $0.02>P>0.01$; similar data were obtained for the decrease in respiratory quotient. Significant decrements in both alveolar ventilation and the per cent increase in alveolar ventilation were noted, $P<0.01$. The change in respiratory rate was not significant, $P>0.05$.

Only one subject was studied with the severest, red obstruction—4.5 mm. diameter. The magnitudes and direction of the changes produced were similar to those noted with the yellow grade of obstruction.

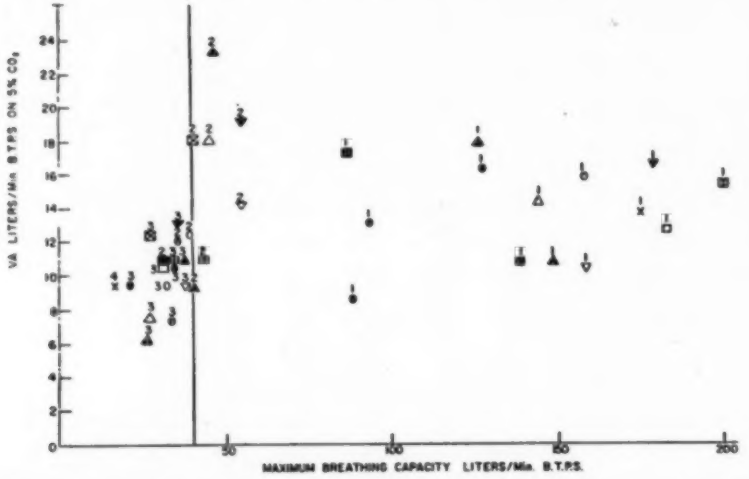

FIGURE 5: Alveolar ventilation on 5 per cent CO_2 inhalation is plotted against maximum breathing capacity. Each symbol represents one subject. The numbers associated with each symbol signify control conditions (1), blue obstruction (2), yellow obstruction (3), and red obstruction (4). The sharp decrease in alveolar ventilation on 5 per cent CO_2 as the maximum breathing capacity falls below 40L./min. is to be noted.

The arterial blood gas data before and during respiratory tract obstruction are given in Table 3. There was no change in arterial oxygen saturation, carbon dioxide tension and pH subsequent to introduction of the blue resistance during inhalation of compressed air and 3 and 5 per cent CO_2, $P>0.05$ for all parameters except the change in arterial oxygen saturation on 5 per cent CO_2 where $0.05>P>0.02$. Interposition of the yellow grade of obstruction produced a significant increment in arterial carbon dioxide tension on 5 per cent CO_2 inhalation, $P<0.01$, and an increment of limited significance on 3 per cent CO_2, $0.05>P>0.02$. The changes in all other parameters of arterial blood gas data were not significant, $P>0.05$. The alterations in arterial blood gas values after insertion of the red obstruction are more pronounced but in the same direction as those after the yellow obstruction.

The differences in control gas exchange and arterial blood gas data in nine subjects studied on two occasions are outlined in Tables 4 and 5. The magnitude of these variations is minimal and not statistically significant except for the change in arterial blood pH on 3 per cent CO_2 and change in arterial blood carbon dioxide tension on 5 per cent CO_2 where $P<0.01$.

These interrelationships are graphically analyzed in Figs. 1 to 6. In Fig 1, alveolar ventilation while inhaling compressed air and 3 and 5 per cent CO_2 in air is plotted on the ordinate and the grades of obstruction on the X axis. The slope of the CO_2 response curve is not appreciably distorted by the blue obstruction. The decrement in slope during the red and yellow obstructions is readily seen. The effect of the various types of obstruction upon the maximum breathing capacity is depicted in Fig 2. In nine subjects, maximum breathing capacity data are available under control conditions and during interposition of the blue and yellow obstructions. The control capacities averaged 112 per cent of predicted (150L./min.); during the blue obstruction the average maximum breath-

TABLE 4—REPRODUCIBILITY OF GAS EXCHANGE DATA AT TWO SEPARATE STUDIES

	$\dot{V}O_2$ (ml./Min./M.²)	R	$\dot{V}E$ (L./Min./M.²)	$\dot{V}E$ per cent Increase vs. Comp. Air	$\dot{V}A$ (L./Min./M.²)	$\dot{V}A$ per cent Increase vs. Comp. Air	f/Min.
Compressed Air							
Average 1	136	.760	4.78		2.23		13.9
2	130	.803	4.80		2.19		14.0
3 per cent CO_2 — 21 per cent O_2							
Average 1	139	.736	7.70	63	3.85	76	16.4
2	135	.764	7.64	60	4.20	95	16.0
5 per cent CO_2 — 21 per cent O_2							
Average 1	147	.752	14.3	208	7.58	253	19.3
2	149	.731	14.2	198	7.20	235	18.6

ing capacity was 33 per cent of predicted (44L./min.); during the yellow obstruction this figure was 24 per cent of the predicted value (32L./min.).

The relationship between alveolar ventilation and the inspired gas concentration of carbon dioxide at the three levels of maximum breathing capacity is shown in Fig. 3 in the nine subjects mentioned above. The slope of the CO_2 response curve is similar at maximum breathing capacities of 150 and 44 L./min.; at a capacity of 32L./min., the slope is patently reduced. The effect of respiratory tract obstruction upon total oxygen consumption in these nine subjects is graphed in Fig. 4. The gross increase in oxygen consumption during 5 per cent CO_2 inhalation (during the yellow obstruction) is to be noted. In both Figures 3 and 4, the control values represent the averaged values in the two control studies, i.e. the control studies before the yellow and blue obstructions in this group of nine subjects.

In Fig. 5, alveolar ventilation on 5 per cent CO_2 (ordinate) is plotted against maximum breathing capacity. The small numbers associated with the various symbols refer to studies under control conditions (symbol 1), during blue obstruction respiration (symbol 2), during yellow obstruction breathing (symbol 3), and during red obstruction respiration (symbol 4). There is little decrease in the alveolar ventilation on 5 per cent CO_2 as the maximum breathing capacity falls until the latter parameter falls below 40L./min. The sharp decrease in alveolar ventilation on 5 per cent CO_2 below this maximum breathing capacity level is readily noted.

In Fig. 6, the per cent increase of alveolar ventilation (on 5 per cent CO_2 compared to compressed air) is plotted against the increment in

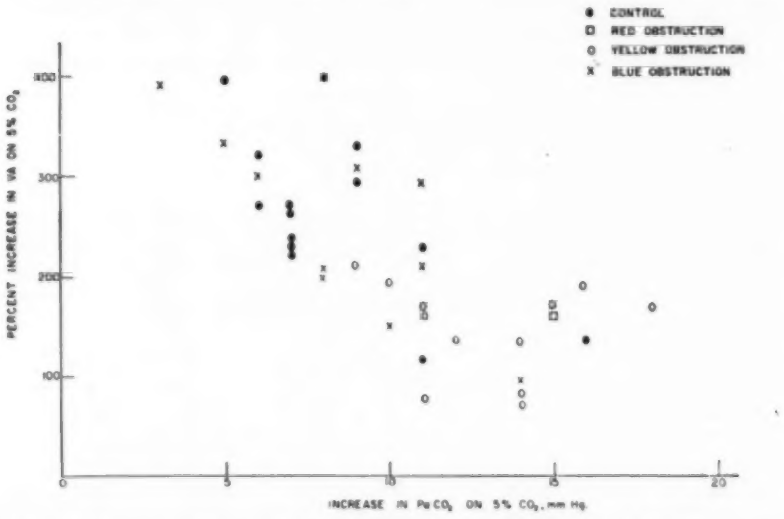

FIGURE 6: Percentage increase in alveolar ventilation (on 5 per cent CO_2 compared to compressed air) is plotted against the increase in arterial blood carbon dioxide tension on 5 per cent CO_2, under the described conditions of respiratory tract obstruction. The limited increment in alveolar ventilation and more pronounced increment in carbon dioxide tension during red and yellow obstruction is evident.

arterial carbon dioxide tension on 5 per cent CO_2. The four symbols are for the varied levels of respiratory tract obstruction. The separation, between the points during control and blue obstruction respiration on the one hand, and between the yellow and red grades of obstruction on the other hand, is to be noted. The increments in alveolar ventilation were smaller and the increments in carbon dioxide tension larger in the latter two groups compared to the control and blue obstruction groups. Similarly, in Fig. 7, per cent increase in alveolar ventilation versus decrement in arterial blood pH, the increment in alveolar ventilation is smaller, and the decrement in arterial blood pH larger for the yellow and red obstruction groups than for the control and blue obstruction subjects.

Discussion

The limited ventilatory response to inhaled carbon dioxide in patients with obstructive pulmonary emphysema and hypercarbia has been noted by many observers.[1-6,8,9] The mechanism of this depressed response may in theory be attributed to:

A. selective depression of the respiratory center response to increased arterial carbon dioxide tension

B. reduction in the maximum breathing capacity

C. increased alkali reserve

Since the administration of diamox may restore the alkali reserve to or toward normal without restoration of CO_2 sensitivity,[1] the third-listed possibility can be eliminated. The second possibility was previously considered unlikely since the average minute ventilation on 5 per cent CO_2 (12.1L./min.) was considerably less than the average maximum breathing capacity (37L./min.) and the average minute ventilation during exercise (19L./min.) in six subjects with emphysema and hypercarbia.[1] Depression of the respiratory center was therefore considered the most likely mechanism.[1-4] Salicylate administration was found to increase the sensitivity of the respiratory center to inhaled CO_2 in normal subjects[10] but not in patients with carbon dioxide retention.[2]

More recently however, evidence has been presented which suggests that a fall in maximum breathing capacity and an increase in the work of breathing may be responsible for the diminished ventilatory response to inhaled CO_2 in subjects with emphysemaand hypercarbia.[5,6] Cherniack and Snidal[6] observed that interposition of an expiratory and inspiratory respiratory tract obstruction in normal subjects resulted in a decreased ventilatory response to inhaled CO_2. In both this normal group of subjects and patients with obstructive pulmonary emphysema, a correlation was observed between the minute ventilation on 5 per cent CO_2 and the maximum breathing capacity. As the latter decreased, a progressive fall in the CO_2 response was observed. Fritts, Fishmanand Cournand[5] found that the increment in the work of breathing on 5 per cent CO_2 was similar in normal subjects and patients with emphysema and hypercarbia when calculated as the increment in work performed per unit increase in arterial carbon dioxide tension when breathing room air and 5 per cent CO_2 (kg.-M./min./mm.Hg. increase in $PaCO_2$). The increment in minute ventilation associated with a given increment in the work of breathing was far less in the emphysematous subjects than in the normal subjects. The concept that alterations in the mechanics of breathing might at least partially explain the diminished ventilatory response to CO_2 (rather than respiratory center depression) was advanced. Recently however, Cherniack[11] has demonstrated that "the total mechanical work of breathing tended to be less in patients with pulmonary emphysema than in the normal subjects, whether expressed as work per liter of ventilation or work per minute," despite the fact that the oxygen cost of ventilation was considerably larger in the emphysematous subject. The lower mechanical work in the latter patients was associated with a markedly reduced efficiency of the respiratory muscles. Zechman, Hall and Hull[12] noted that graded resis-

TABLE 5—REPRODUCIBILITY OF BLOOD GAS DATA AT TWO SEPARATE STUDIES

	Compressed Air			3 per cent CO_2 - 21 per cent O_2			5 per cent CO_2 - 21 per cent O_2		
	SaO_2 per cent	$PaCO_2$ (mm.Hg.)	pH	SaO_2 per cent	$PaCO_2$ (mm.Hg.)	pH	SaO_2 per cent	$PaCO_2$ (mm.Hg.)	pH
Average 1	96.6	40.6	7.394	98.6	45.7	7.362	99.4	49.5	7.336
2	96.0	41.8	7.391	98.1	46.2	7.355	98.7	51.1	7.322

tance to tracheal air flow in man resulted in an increase in the work of breathing and a fall in pulmonary ventilation, a rise in alveolar carbon dioxide tension, and a fall in alveolar oxygen tension. Similar observations have been made in the experimental animal[13] in spite of the augmented muscular activity associated with tracheal obstruction.

The present study was designed to delineate the effect of respiratory tract obstruction upon the ventilatory response to CO_2 more completely by a simultaneous study of the ventilatory and gas exchange functions of the lung. The results suggest that the relationship between the reduction in maximum breathing capacity and the reduction in ventilatory response to CO_2 is not linear. That is, in Fig. 5, a decrease in maximum breathing capacity is not associated with a fall in alveolar ventilation on 5 per cent CO_2 until a critical value of 40L./min. is reached. These data are not in agreement with those of Cherniack and Snidal.[6] It is of considerable interest that Froeb, et al,[14] in a study of the induction of respiratory acidosis by oxygen breathing, found that respiratory acidosis (defined as a fall in arterial blood pH below 7.38) appeared only in those subjects who had maximum breathing capacities below 40 to 50 per cent of the predicted values. The relationships in Figs. 6 and 7 also demonstrate that the blue ("mild") obstruction produced little effect upon the ventilatory response to CO_2 in these normal subjects except for a decrease in respiratory rate. The effect of the higher grade red and yellow obstruction is most apparent at the 5 per cent CO_2 level, Tables 2 and 3. The data in Fig. 2 illustrate the pronounced effect of the mild blue obstruction upon maximum breathing capacity. Despite the latter observation, the CO_2 response curves in Fig. 1 demonstrate the limited effect of the mild blue obstruction. This observation is repeated in Fig. 3 where it is noted that a fall in maximum breathing capacity from 150L./min. to 44L./min. is associated with no significant change in the ventilatory response to CO_2. A modest further fall in breathing capacity to 32L./min. however results in a sharp fall in alveolar ventilation on 5 per cent CO_2.

These results suggest that abnormal ventilatory mechanics may in part at least be associated with a diminished response to inhaled CO_2 both in normal subjects and emphysematous subjects. As suggested by Riley,[15] the organism may tolerate an increase in arterial blood carbon dioxide tension in preference to an undue expenditure of available oxygen for ventilatory purposes—as illustrated by the oxygen consumption data in Fig. 4.

Abnormal respiratory mechanics cannot however be the sole factor responsible for the diminished ventilatory response in patients with emphysema and hypercarbia. Three lines of evidence suggest that other factors, i.e. a diminished respiratory center sensitivity may also be of importance. First, the ventilatory response to inspired CO_2 may be normal despite an increased work of breathing in subjects in cardiac failure,[16] and in patients with pulmonary fibrosis.[17] On the other hand, the CO_2 response may be relatively normal despite a marked reduction in maximum breathing capacity.[1,4] In P.G.,[1] Table 1, the minute ventilation on 5 per cent CO_2 (17.2L./min.) was virtually identical to the maximum breathing capacity. The control $\dot{V}_E$ on room air was 6.50L./min. Hypercarbia was absent in this patient. Gilbert *et al.*[18] have investigated the respiratory response to inhaled CO_2 in obese subjects. A diminished response to inhaled CO_2 was observed in 5 such patients. No correlation was found between the separately determined oxygen cost of breathing and the depressed CO_2 response.

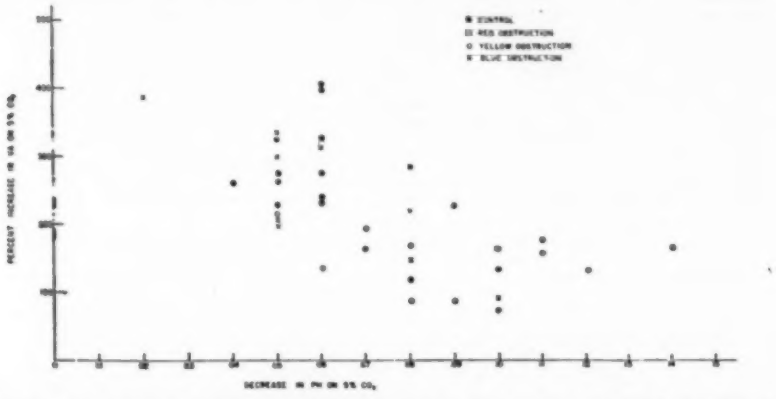

FIGURE 7: Per cent increase in alveolar ventilation (on 5 per cent CO_2 compared to compressed air) is plotted against the decrease in arterial blood pH on 5 per cent CO_2. The changes during control studies and blue obstruction are readily separable from those during yellow and red obstruction.

Secondly, the ventilatory response to inhaled CO_2 may be impaired in normal subjects by an extended stay in an environment enriched with CO_2.[19] Thirdly, several reports[20-22] have appeared describing patients with alveolar hypo-ventilation secondary to a damaged respiratory center. These latter patients had normal lungs, normally functioning chest bellows and normal respiratory mechanics.

The studies reported to date suggest that both factors, i.e. respiratory center depression and abnormal ventilatory mechanics, play a role in the pathogenesis of the depressed ventilatory response to inhaled CO_2 in patients with emphysema and hypercapnia.

SUMMARY

The effect of both inspiratory and expiratory respiratory tract obstruction upon the ventilatory response to 3 and 5 per cent CO_2 has been studied in 14 normal subjects. Three grades of obstruction were employed. In nine subjects the effects of two levels of obstruction were noted. Maximum breathing capacities were determined under both control and experimental (respiratory tract obstruction) conditions.

The results indicate that mild degrees of obstruction have relatively little effect upon the response to inhaled CO_2. A decrease in alveolar ventilation and arterial blood pH and an increase in arterial carbon dioxide tension result from interposition of more severe grades of obstruction. The etiology of the depressed ventilatory response to inhaled CO_2 seen in patients with obstructive pulmonary emphysema and hypercarbia is discussed in relation to these experimental observations.

RESUMEN

El efecto de la obstrucción tanto expiratoria como inspiratoria en las vías respiratorias sobre la respuesta ventilatoria a 3 y 5 por ciento de CO_2 se ha estudiado en los sujetos normales. Se emplearon tres grados de obstrucción. En nueve individuos los efectos de dos niveles de obstrucción se notaron. Las capacidades respiratorias máximas se determinaron tanto bajo control como experimentalmente (obstrucción del tracto respiratorio).

Los resultados indican que los grados moderados de obstrucción tienen relativamente pocos efectos sobre la respuesta al CO_2 inhalado. El decrecimiento de la ventilación intra alveolar y del pH de la sangre arterial y el aumento de la tensión arterial del bióxido de carbono son el resultado de la interposición de mas acentuados grados de obstrucción.

La etiología de la respuesta ventilatoria deprimida al CO_2 inhalado observado en enfermos con enfisema pulmonar obstructivo e hipercarbia se discuten en relación con estas observaciones experimentales.

RESUMÉ

L'effet de l'obstruction des voies respiratoires à la fois inspiratoire et expiratoire sur la réponse ventilatoire de 3 à 5% de gaz carbonique, a été étudié chez 14 sujets normaux. Trois degrés d'obstruction furent employés. Chez 9 sujets, les effets de deux taux d'obstruction furent notés. La capacité respirattoire maximum fut déterminée sous des conditions de contrôle et d'expérimentation (obstruction des voies respiratoires).

Les résultats indiquent que l'obstruction peu importante a un effet relativement faible sur la réponse au gaz carbonique inhalé. Une diminution de la ventilation alvéolaire et du pH du sang artériel, et une augmentation de la tension du gaz carbonique artériel résulte de l'utilisation d'obstruction d'une importance plus grande. La cause de la diminution de la réponse ventilatoire au gaz carbonique inhalé chez les malades atteints d'emphysème pulmonaire obstructif et d'hypertrophie cardiaque est discutée, en liaison avec ces observations expérimentales.

ZUSAMMENFASSUNG

Es wurde der Einfluß eines-sowohl respiratorisch als auch expiratorisch wirksamen-Verschlusses des Respirationstraktes auf die ventilatorische Reaktion gegenüber 3 und 5% CO_2 an 14 normalen Versuchspersonen geprüft. Drei Grade des Verschlusses gelangten zur Anwendung. Bei 9 Personen wurden die Wirkungen von zwei Stufen des Verschlusses beobachtet. Atemgrenzwert wurde sowohl unter den Versuchsbedingungen (Verschluß des Respirationstraktes) wie auch bei Kontrollen bestimmt.

Die Resultate deuten daraufhin, daß leichte Grade des Verschlusses verhältnismässig wenig Einfluß auf die Reaktion gegenüber inhaliertem CO_2 haben. Ein Rückgang der alveolären Ventilation und des arteriellen Blut-pH, sowie ein Anstieg der arteriellen CO_2-Spannung, ergeben sich aus dem Eingreifen schwerer Formen von Verschluß. Diskussion über die Ätiologie der verlängerten ventilatiorischen Reaktion gegenüber inhaliertem CO_2, wie man sie bei Kranken mit obstruktivem Lungenemphysem und Hypercarbie sieht, in Bezugauf diese experimentelle Beobachtungen.

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STAPHYLOCOCCAL ANTIBODIES IN CYSTIC FIBROSIS OF THE PANCREAS

The association of Staphylococcus aureus with the lung infections that such patients reveal is probably due to changes in the physicochemical behavior and perhaps in chemical structure of bronchial mucus. These factors may either furnish the ever-present strains of Staphylococcus aureus with a suitable nidus for invasion, or, they may interfere with the normal defense mechanisms in this area.

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Report on the Use of Cycloserine and Isoniazid in Twenty-seven Cases of Pulmonary Tuberculosis in Psychotic Patients

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The majority of physicians engaged in pulmonary diseases recognizes the practical need for additional drug regimens, especially in the tuberculous psychotic patient. The usual drug combinations in recent years have been, viz: isoniazid-PAS, isoniazid-streptomycin, or streptomycin-PAS.

There is a frequent appearance of drug resistance to streptomycin, as well as occasional toxic side effects. The frequent and rather severe gastro-intestinal upsets are produced by PAS. Last is the fact that isoniazid alone is not satisfactorily effective in adult pulmonary tuberculosis, unless an efficient ancillary drug is added to it.

In this condition a regimen of isoniazid and cycloserine has been found to be useful and the results of treatment in 27 cases at the State Mental Hospital, Logansport, Indiana, have been sufficiently encouraging to warrant analysis and publication.

Practically all of the patients were chronic cases, having an average duration of anti-tuberculosis treatment of 5.5 years and all in the group had received prior anti-tuberculosis chemotherapy for one year or longer. Six patients in the group had received therapeutic pneumoperitoneum; two had had temporary phrenic crush; three had had thoracoplasty; and one had resectional surgery (lobectomy) after treatment with the drug regimen. In addition, all had been under intensive antituberculosis chemotherapy for prolonged periods of time with the three standard regimens of streptomycin-PAS, isoniazid-streptomycin, or isoniazid-PAS. These had been interchanged according to intolerance or toxic side effects.

The average dose in the majority of cases has been two capsules a day (each with a combination of 250 mgm. cycloserine and 150 mgm. of isoniazid, making a total daily dosage of 500 mgm. cycloserine and 300 mgm. of isoniazid). Medication had to be discontinued in only two patients; one because of grand mal convulsions with abnormal electroencephalogram findings, and the other because of marked depression with suicidal tendencies.

At the time, when the report was compiled, this combination of drugs had been in constant use by three patients for a period of 15 to 26 months; by 20 for a period of five to 15 months; and by another four for a period of less than five months.

In one, streptomycin was added to the treatment schedule, due to postoperative spread with hemorrhage following right thoracoplasty. In three cases, PAS, 6 grams daily, was added (one due to extensive bilateral toxic disease, two because of bilateral increase while on the treatment schedule).

Six patients with far-advanced disease died while under treatment (two from acute hypostatic pneumonia, one from acute cardiac failure while on the operating table, two from debility with extensive far advanced disease with tuberculous laryngitis, and one with coronary infarction). In other words, none of the deaths was attributable to the treatment schedule.

Two patients in the series improved sufficiently to have surgery (one thoracoplasty and one lobectomy) while on the treatment schedule. These had been unable to do so on the three standard regimens of chemotherapy.

Carefully evaluating the clinical progress in the series, improvement was definitely noted in 19 of the 27 patients (70 per cent). In two the disease remained static, the clinical symptoms changing insignificantly under this treatment. Only six of the 27 (22.5 per cent) have shown a distinct decline with increase in the disease.

Tubercle bacilli disappeared from the sputum or gastric culture in five cases. This is considered a good result, since the series consisted chiefly of patients with long-standing chronic disease who had received the usual three standard regimens before being put on cycloserine-isoniazid.

Evaluating progress by roentgenography, it was found that in 15 of the 27 cases there had been definite improvement, although it was only slight or initial in three of the 15 cases. In another nine cases of the series, there was no significant roentgenographic change, the picture revealing neither spread nor improvement. In only three cases of the series was the disease marked as being worse and one of them died from far-advanced disease with associated laryngitis three months after being started on the regimen.

In further evaluating the clinical findings, it was found that the general well-being was distinctly improved in 11 of the 27 cases; the appetite improved in 10 cases; the weight increased in 11 cases, but five of the patients lost weight despite the treatment. Most of them were afebrile. Reduction of cough was noted in 12 cases; reduction in expectoration was noted in an equal number of cases. Two extra-pulmonary tuberculous complications were included in this series, one of tuberculous laryngitis and one with tuberculous empyema following spontaneous pneumothorax.

In checking for unpleasant side effects, it was found that two complained of drowsiness. Grand mal convulsions were noted in one and marked depression with suicidal tendencies in one.

Prior to initiating cycloserine-isoniazid therapy, the following laboratory studies were done, viz: hemograms, urinalysis, 15-minute PSP, BUN, cephalin flocculation, electrocardiogram, electroencephalogram, sputum or gastric culture, x-ray films of the chest. X-ray films of the chest, hemograms and urinalysis were done every two months. The ECG, EEG, BUN, PSP and cephalin flocculation were repeated at the end of treatment. There was no significant change in the hemograms; nitrogen retention did not interfere with the treatment in any case. One

case showed an abnormal EEG during the course of treatment, which along with the association of grand mal type of convulsions caused the treatment to be terminated.

Pre-existing complicating diseases did not seem to interfere with the treatment, except in one who developed marked depression with suicidal tendencies which necessitated discontinuing the treatment. Among the complications noted were asthma, moderate arthritis, cardiac conditions and peripheral vascular disease.

SUMMARY

Twenty-seven psychotic patients with pulmonary tuberculosis have been treated with cycloserine-isoniazid for periods as long as 26 months. The majority of them had advanced disease of several years' duration and had previously received three standard drug regimens. Some of them had been treated by compression or resectional surgery. Significant improvement was noted in a gratifying percentage of the patients. Reversal of infectiousness occurred in a satisfactory number; roentgenographic improvement was observed in a fair percentage; many showed improvement in well-being and appetite; there was a fairly satisfactory reduction in cough and expectoration. Complicating side effects have been fairly slight, particularly in view of the fact that all of the patients were psychotic. From this clinical experience, it is concluded that a regimen of 500 mgm. of cycloserine and 300 mgm. of isoniazid daily, in two equally divided doses, is a valuable regimen for psychotic patients who still have active disease despite treatment with one of the standard regimens.

ACKNOWLEDGEMENT: Cycloserine was supplied as Seromycin by Eli Lilly and Company, Indianapolis, Indiana.

RESUMEN

Veintisiete enfermos de tuberculosis pulmonar y además psicóticos, se trataron con cicloserina e isoniacida por tiempos hasta de 26 meses.

La mayoría de ellos tenían le enfermedad avanzada, de various años de curación y habían recibido antes los regímenes de drogas habituales.

Algunos de ellos habían sido tratados por compresión o resección. Se notó una mejoría de significación en un número satisfactorio de enfermos. La desaparición de la infecciosidad se observó en un número de enfermo satisfactorio; la mejoría radiológica se vió en un porcentaje mediano; muchos mostraron mejoría general y del apetito; hubo alguna reduccion de la tos y de la expectoración. Los efectos colaterales complicantes han sido sensiblemente ligeros particularmente en vista de todos los enfermos eran psicóticos. Según esta experiencia clínica se concluye que el régimen de 500 mg. de cicloserina y 300 mg. de isoniacida por día en dos dosis iguales dividida es valioso en los enfermos psicóticos que aún tienen enfermedad activa a pesar del tratamiento con las otras drogas comunmente usadas.

RESUMÉ

L'auteur rapporte 27 cas de tuberculose pulmonaire chez des malades atteints de troubles psychiques, traités par la cyclosérine et l'isoniazide pendant des périodes s'étendant jusqu'à 26 mois. La majorité d'entre eux avaient des lésions avancées datant de plusieurs années, et avaient été antérieurement traités par les trois médications standard. Certains d'entre eux ont été traités par collapsothérapie ou par résection chirurgicale. Une amélioration importante fut notée dans une proportion satisfaisante de l'ensemble des malades. La suppression de l'infection apparut dans un nombre de cas satisfaisant; une amélioration radiologique fut observée dans une bonne proportion; plusieurs montrèrent une amélioration du comportement et de l'appétit; il y eut une réduction vraiment satisfaisante de la toux et de l'expectoration. Les effets toxiques secondaires ont été bien légers, particulièrement si l'on considère qu'il s'agissait de malades atteints de troubles psychiques. De cette expérience clinique, l'auteur conclut qu'un programme thérapeutique de 500 mmg. de cyclosérine par jour et 300 mmg. d'isoniazide, en deux doses égales, est une thérapeutique valable pour les malades mentaux dont l'affection est encore active malgré le traitement avec les médications habituelles.

ZUSAMMENFASSUNG

Es wurden 27 Kranke mit Lungentuberkulose unter psychotischen Patienten mit Cykloserin und INH für Zeitspannen in einer Länge bis zu 26 Monaten behandelt. Bei der Mehrzahl von ihnen fanden sich fortgeschrittene Krankheitsformen von mehrjähriger Dauer, und zuvor war eine Behandlung mit dem Standard-Drei-Medikamenten-Schema durchgeführt worden. Einige von ihnen hatten eine Kollapstherapie

oder Resektionen erhalten. Eine signifikante Besserung war bei einer erfreulichen Zahl der Kranken festgestellt worden. Zu einer Beseitigung der Ansteckungsfähigkeit kam es in einer befriedigenden Zahl, röntgenologische Besserung wurde in einem leidlichen Prozentsatz ermittelt; viele zeigten eine Besserung ihres Allgemeinzustandes und Appetites; es kam auch zu einem zufriedenstellenden Rückgang von Husten und Auswurf. Komplizierende Nebenwirkungen waren einigermaßen gering, besonders im Hinblick auf die Tatsache, daß es sich bei sämtlichen Fällen um Geisteskranke handelte. Man kann aus dieser Erfahrung schliessen, daß eine Verordnung von 500 mg Cykloserin und 300 mg INH täglich, auf zwei gleiche Dosen verteilt, ein wirksames Vorgehen darstellt für psychotische Kranke, deren Prozess trotz Behandlung mit einer der Standardverfahren noch aktiv geblieben ist.

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ELECTRON MICROSCOPY: THE INVASIVE PROPERTIES OF MALIGNANT NEOPLASMS, INCLUDING THE LUNG

Study of the early stages of malignant neoplastic growths with electron microscopy provides data that elucidate the mechanism of invasion. There are found deficiencies of intercellular connecting processes and evidence of decreased cell cohesiveness among the malignant cells. Loss of basement membrane is also demonstrable at sites of early invasion of malignant epithelial tumors. The process of early invasion is depicted as primary loss of basement membrane, decreased cell cohesiveness, and protrusion first of cytoplasm, then of an entire tumor cell into adjacent connective tissue spaces.

It is suggested that the property of invasiveness, based partially upon the described structural characteristics, comprises a major distinguishing characteristic of malignant neoplasia.

Ashworth, C. T., Luibel, F. J., and Sanders, E.: "Electron Microscopy, The Invasive Properties of Malignant Neoplasms," *Texas J. Med.*, 56:851, 1960.

Effect of Propyliodone (Dionosil[R]) Bronchograms on Blood Iodine and Radioiodine Uptake

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Elevation of blood iodine may be caused by hyperthyroidism or the previous administration of iodine-containing compounds, among other things.[1-6] Means[7] noted "the prolonged 'spurious' elevation of protein-bound iodine which follows the administration of such organic iodine-containing compounds as iodophthalein sodium (Iodeikon[R]) or iodized poppyseed oil (Lipiodol[R]) used in roentgenography." Salter[8] stated that "the intrathecal injection of Lipiodol may form a localized reservoir of iodine which will slowly feed small amounts of iodine into the general circulation over the course of many weeks."

A previous study reported in 1949[9] revealed that bronchograms using Lipiodol affected protein-bound iodine (PBI) values greatly. Levels of more than 400 micrograms per 100 ml. of blood were secured during the first week after the bronchogram. PBI values fell gradually averaging 30 micrograms at six months, 14 micrograms per 100 ml. of blood at 12 months, and reaching normal values 17 months after the Lipiodol bronchograms, although individual patients maintained elevated PBI values for three and four years.

Dionosil

The use of organic iodine compounds to visualize the bronchial tree was suggested by Waters, Bayne-Jones, and Towntree in 1917. Sicard and Forestier used Lipiodol for bronchograms in 1922. The main disadvantage was retention of iodized oil within the alveoli for long periods of time, even years, and interference with the interpretation of subsequent chest roentgenograms. Tomich *et al.*[10] reasoned that a suspension of contrast medium slightly soluble in body fluids would be advantageous by permitting rapid clearance from the bronchi and lung. Propyliodone (Dionosil[R]) was found to be very satisfactory.

Dionosil is a suspension of n-propyl ester of 3:5-diiodo-4-pyridone-N-acetic acid. We have used only Dionosil Oily which is a 40 per cent W/V suspension in peanut oil. The iodine content is 34 per cent and there are about 7 grams of iodine in a 20 ml. vial. Tomich *et al.*[10] reported that the material did not enter the alveoli of experimental animals and there was no evidence of toxicity. The oil was eliminated from the lungs within five days. Animal experiments with I^{131}—labeled propyliodone and human metabolism studies revealed the compound to be completely hydrolyzed and eliminated through the kidneys without breakdown to iodine or iodides. Numerous clinical reports[11-16] attest to its safety, east of instillation, lack of toxicity, absence of iodism, and satisfactory bronchograms. Histologic examinations of lung tissue excised after bronchography have revealed no granulomata.[12,17]

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The rapid elimination of Dionosil and the absence of iodine formation are definite advantages in bronchography. The n-propyl ester in Dionosil is hydrolyzed within a few days, absorbed into the blood and excreted in the urine. Although the rapid clearing of Dionosil from the bronchi is readily apparent on serial roentgenograms, the exact effect of Dionosil on PBI and iodine metabolism is unknown and was deemed worthy of study. The parameters selected as rough indices of changes in the iodine pool were radioiodine uptake (RAI) and PBI.

Study

Twenty-five apparently euthyroid patients each requiring a bronchogram were evaluated with respect to thyroid function. Protein-bound iodine, and 24-hour radioiodine uptake studies were normal prior to bronchography. The patients were included in the study only if thyroid function was determined to be normal, and if no exogenous iodides in the form of expectorants and contrast media had been administered within the previous six months. In most instances the pre-bronchogram

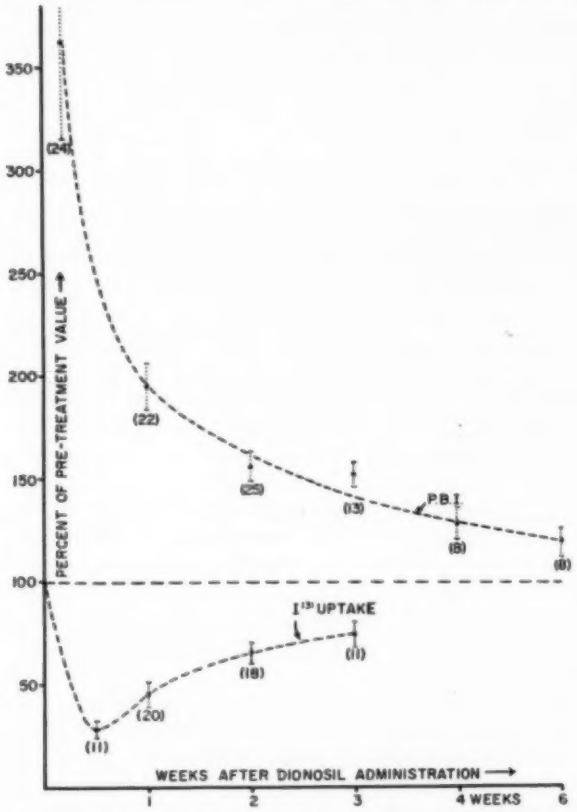

FIGURE 1: Course of PBI and I^{131} uptake after Dionosil administration plotted as per cent of pre-treatment value with standard error of the means. Number of analyses are in parentheses. Distribution around each point is indicated by the vertical dotted line.

I^{131} uptake and PBI were done within a week prior to administration of Dionosil, and the post-Dionosil studies were performed three days following bronchography. The determinations were then repeated at weekly intervals for as long as six weeks in some cases.

Serum protein-bound iodine analysis was performed by the method of Brown, *et al.*[15] modified by Carl Buchholz, who simplified the procedure by consolidating several reagents. The Somogyi method of protein precipitation which was employed has been shown to remove all but 1 to 2 per cent of inorganic I^{131} added to serum. The normal range for this laboratory is 3.8 to 8 micrograms per cent.

RAI uptake was performed in the following manner: patients received 10 microcuries of I^{131} and 24 hours later the per cent of the administered dose was determined by counting with a scintillation detector and an appropriate scaler. At the time each test was performed, each patient was questioned as to the possible receipt of iodide-containing medication. If such had occurred he was excluded from the study. Changes in PBI and radioiodine uptake are graphed in the form of per cent of pre-treatment values (Fig. 1).

Bronchography was then performed with filling of the bronchi of suspected areas of disease, usually both lower lobes, right middle lobe, and lingula of the left upper lobe.

Bronchogram Procedure

Preliminary postural drainage was performed if copious sputum was present. Preliminary orders included: (1) no lunch, (2) secobarbital (Seconal^{R}) 0.1 gm. orally, and codeine phosphate 0.03 gm. hypodermically, each one hour before the instillation of radio-opaque oil. Solution Dyclone^{R} 0.5 per cent (4-n-butoxy-beta-piperidinopropiophenone hydrochloride) was applied topically to the mucous membranes of the pharynx and larynx. Usually about 15 ml. were required. A rubber catheter was introduced through the larynx into the trachea and Dionosil Oily injected. 20 ml. at room temperature were usually used, and the patient was postured for proper mapping of the bronchial tree. Prophylaxis with antibiotics and sensitivity tests with Dionosil are unnecessary as routine procedures, and were not performed.

Results

The PBI approached, but did not always return to control levels within six weeks of Dionosil administration (Fig. 1). The radioiodine uptake was suppressed immediately after Dionosil and at the end of three weeks had not reached 100 per cent of the control values. Although at the time intervals mentioned the PBI and radioiodine uptake results were within or close to the normal for this laboratory, one must conclude that there was minor expansion of the iodide pool by Dionosil at the end of six weeks.

Discussion

Oily Dionosil is safe and produces excellent bronchograms. There appears to be no danger of tissue reaction or granuloma formation. The PBI is much less affected by a Dionosil bronchogram than by a Lipiodol bronchogram. The blood PBI after Dionosil

usually returns to or close to the normal range after about six weeks, although it would be best to wait at least eight weeks after bronchography, before performing PBI determinations for thyroid studies.

The radioiodine uptake began rising toward the normal range within one week of Dionosil administration and at the end of three weeks fell within the normal range for this laboratory. This indicates that the radioiodine uptake would be a valid parameter of thyroid function three weeks after Dionosil bronchography.

SUMMARY

1. Oily Dionosil is a safe and satisfactory agent for bronchography. Excellent visualization is secured usually.

2. Oily Dionosil produces elevation of the serum PBI (usual initial range is 9 to 23 mcg./100 ml. serum), with return to the normal range of 3.8 to 8 mcg./100 ml. serum in about six to eight weeks.

3. PBI determinations which may be required after Dionosil bronchography are best postponed until eight weeks after bronchography.

4. Radioiodine uptake determinations should be postponed until at least three weeks after Dionosil bronchography.

ACKNOWLEDGEMENT: Grateful acknowledgement is made to Carl Buchholz for PBI determinations, Mrs. Judy Johnson and Margaret Bates for secretarial assistance, and Timothy P. Dodge and Robert T. Harrison of Medical Illustration Service.

RESUMEN

1. El Dionosil oleoso es un medio satisfactorio y seguro para broncofrafía. Generalmente se obtiene una visualización excelente.

2. Produce una elevación del PBI en el suero (generalmente la tasa inicial es de 9 a 23 microgms. por ml. de suero) y regresa a lo normal de 3.8 - 8 mcgms. por ml. en seis a ocho semanas.

3. Las determinaciones de PBI que pueden requerirse después del uso del Dionosil en broncografía deben preferiblemente postponerse hasta ocho semanas después del procedimiento.

4. Las determinaciones de yodoradioactivo deben posponerse hasta después de tres semanas después de la broncoscopía de Dionosil como término minimo.

RESUMÉ

1. Le "Dionosil huileux" est un produit sans risque donnant des résultats satisfaisants en bronchographie. Il provoque actuellement une excellente visualisation.

2. Le Dionosil huileux produit une élévation des protéines du sérum marquées à l'iode (le taux initial habituel est de 9 à 23 mcg. pour 100 ml. de sérum) avec retour aux taux normal de 3.8 à 8 mcg./100 ml. de sérum en six à huit semaines environ.

3. Il est préférable de reporter les déterminations des protéines marquées à l'iode, que peuvent être nécessitées après bronchographie par le Dionosil à huit semaines après la bronchographie.

4. Les contrôles par iode radio-actif devraient être reportés à au moins trois semaines après bronchographie par le Dionosil.

ZUSAMMENFASSUNG

1. Dionosil in öliger Lösung ist ein sicherer uund befriedigender Stoff für die Bronchographie. Für gewöhnlich ist eine ausgezeichnette Kontrastdarstellung gewährleistet.

2. Öliges Dionosil führt zu einem Anstieg des Serums PBI (die gewöhnlichen Eingangswerte liegen bei 9 - 23 cbmm auf 100 ccm Serum), mit Rückkehr zu normalen Werten von 3.8 - 8 cbmm/100 ccm Serum im Verlauf von 6 - 8 Wochen.

3. PBI-Bestimmungen, die nach einer Bronchographie mit Dionosil erforderlich werden können, werden am besten bis 8 Wochen nach der Bronchographie verschoben.

4. Bestimmungen der Aufnahme von radioaktivem Jod müssen aufgeschoben werden bis mindestens 3 Wochen nach der Dionosil-Bronchographie.

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METHODS OF RETROGRADE AORTOGRAPHY THROUGH BRACHIAL ARTERY IN PATIENTS WITH THE COARCTATION AND AORTIC ANEURYSMS

The authors report methods of retrograde aortography through brachial artery which was performed in 20 patients with coarctation of the aorta and in four patients with aortic aneurysms. The investigation was carried out under local anesthesia with 9.5 per cent novocain solution. This method by means of inserting a catheter into aortic portions changed pathologically contributes to better determination of their hemodynamic state by plotting pressure curves and also to gaining some knowledge as to the condition of the aortic walls, size and location of the aneurysms.

Rapid injection of the contrast substance into the affected portion provides in all cases distinct outlines in serial aortograms. In one case, complications have been observed. The authors conclude that the described technic should be a technic of choice in coarctation of the aorta and aortic aneurysms.

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Sarcoidosis: Clinical and Thoracic Roentgen Features*

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I. *Introduction*

Sarcoidosis is a disease that may involve practically any organ in the body thus giving rise to many clinical syndromes. We have shared in the general interest of the protean manifestations of sarcoidosis and have recently analyzed our clinical experiences. This review comprises 45 cases of sarcoidosis. Forty (89 per cent) are living as of September, 1958 when this analysis was made. The length of follow-up in the living cases is: less than six months—three cases; one year through four years—13 cases; five years through nine years—18 cases; 10 through 14 years—three cases; 15 to 18 years—three cases. The remaining 5 (11 per cent) died and the length of survival ranged from two to nine years.

II. *Material*

The charts of patients admitted to the hospital and its affiliated chest clinics, wherein the diagnosis of sarcoidosis was mentioned, were reviewed and after careful scrutiny were accepted for inclusion in this study if there was histologic confirmation of the diagnosis; or if in the absence of such confirmation, prolonged observation on the basis of clinical and/or laboratory and roentgenological findings made the diagnosis a sound and tenable one. Serial chest roentgenograms were available on all patients.

The final yield was a total of 45 cases. Of these, 20 (44 per cent) had a histologic diagnosis. The sources for this confirmation were: (a) lymph node biopsy—11 cases; (b) lung biopsy—three cases; (c) skin biopsy—three cases; (d) autopsy—two cases; (e) naso-pharyngeal mucosal biopsy—one case. Thirty cases (66 per cent) of the total had one or more hospital admissions. Follow-up information has been obtained in a few instances from private physicians.

III. *Analysis of Clinical Features*

(A) *Epidemiologic Data:* The cases were about equally divided between the colored (23) and the white races (22). Twenty-five (56 per cent) were women. The age at the time of diagnosis ranged between 19 to 49 years and the average age was 32. All were long-time residents in the Hudson County area.

(B) *Symptomatology:* Inasmuch as these patients had a chronic course, the clinical findings at any given time do not adequately portray the full vista of symptoms and signs. Emphasis has therefore been placed on clinical situations which *first* brought the patient to the atten-

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tion of a physician. Analysis of the symptom complex which precipitated the patient's *first* admission to the hospital or clinic indicated that: (1) 32 (71 per cent)* had pulmonary symptoms—cough was present in 21 cases, dyspnea in 11 and wheezing in two; (2) three (7 per cent) had extra-pulmonary symptoms, referable to other organs; (3) 21 (47 per cent) had constitutional symptoms—fatigability and weight loss were the most common; (4) 10 (22 per cent) were completely asymptomatic and these cases were detected on the basis of a routine chest x-ray film.

(C) *Physical Examination:* Almost any tissue or organ may be involved at one time or another in sarcoidosis. The frequent lack of correlation between thoracic symptomatology and objective findings on physical or roentgen examinations of the chest noted by many observers was also confirmed in this series. The following sites of extra-thoracic abnormalities were detected either on admission or during the clinical course of the disease: (a) enlarged superficial lymphnodes (discrete and non-tender)—19 cases (44 per cent). The distribution of these was—cervical 11 patients, axillary seven, inguinal six, epitrochlear five, significant decrease in the size of the nodes occurred in 11 patients; (b) skin lesions—seven (16 per cent). Six cases had erythematous plaque-like non-puritic lesions. The lower extremities were the commonest location. One had a fairly generalized vesicular and papular eruption. These lesions did not disappear during the period of clinical observation; (c) hepato-splenomegaly—two cases (9 per cent). No regression was noted on later examinations; (d) bone lesions—three (7 per cent). These consisted of cystic changes (detected on x-ray film examination only) in the extremities. The lesions persisted; (e) occular lesions—two (4 per cent). These two had uveitis. One proved refractory to steroid therapy and

*Note: Percentage figures throughout are expressed in terms of round numbers.

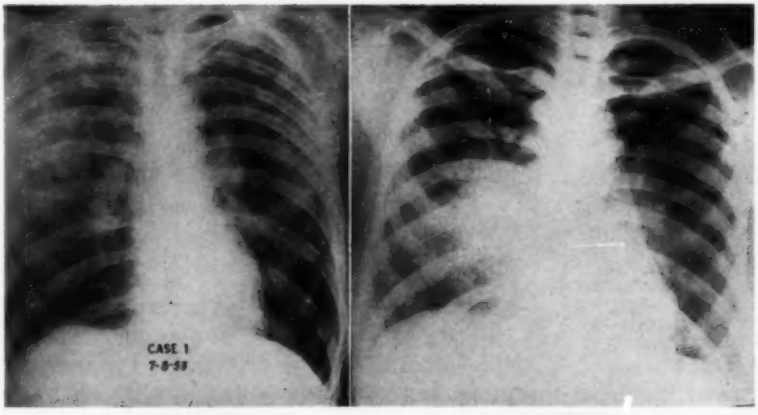

FIGURE 1 FIGURE 2

FIGURE 1: White man, age 49—x-ray film (July 8, 1953) revealed densely packed bilateral miliary foci; lung biopsy compatible with sarcoidosis. FIGURE 2: Colored man, age 45—x-ray film (July 28, 1941) revealed bilateral predominantly miliary foci with bronchopulmonary and mediastinal adenopathy; axillary node biopsy compatible with sarcoidosis.

subsequently became blind; (f) parotid gland involvement—two (4 per cent). Involution to normal size occurred in both instances; (g) involvement of naso-pharyngeal mucosa—one case.

IV. *Analysis of Thoracic Roentgen Features*

The increasingly widespread use of roentgenography has uncovered unsuspected or asymptomatic instances of pulmonary sarcoidosis which may produce the most impressive evidence of this condition. While it is difficult to establish arbitrary lines of demarcation, it may be of interest to record the predominant chest x-ray film findings *at the time the diagnosis was first made* in this series of cases. All of the cases had abnormal roentgenologic findings which were classified as follows: (A) the miliary or small nodular parenchymal lesion (bilateral) without adenopathy (hilar and/or mediastinal)—four cases (9 per cent) (Fig. 1); (B) the miliary or small nodular parenchymal lesion (bilateral) with adenopathy—12 cases (27 per cent) (Fig. 2); (C) the linear parenchymal lesion (bilateral) without adenopathy—three (7 per cent) (Fig. 3); (D) the linear parenchymal lesion (bilateral) with adenopathy—11 (24 per cent) (Fig. 4); (E) the mixed parenchymal lesion (bilateral) consisting of miliary or small nodular foci together with linear or confluent areas of infiltration but *without* adenopathy—12 cases (27 per cent) (Fig. 5); (F) adenopathy (hilar and/or mediastinal) but without parenchymal involvement—three (7 per cent) (Fig. 6). It is thus seen that at the time of diagnosis about 58 per cent of the cases had intrathoracic adenopathy and 93 per cent showed parenchymal involvement which was bilateral in all and symmetrically distributed in nearly all cases.

TABLE 1—SARCOID PATIENTS WHO RECEIVED STEROIDS

Patient	Indication	Agent Used	Duration of Rx (months)	Result obtained during Rx
L.B.	Dyspnea	Hydrocortisone	3½	Marked symptomatic improvement, but no significant change on x-ray film
A.C.	Dyspnea	Hydrocortisone	9	Moderate symptomatic improvement, but no significant change on x-ray film
L.K.	Dyspnea	Hydrocortisone	3	Moderate symptomatic improvement, but no significant change on x-ray film. Symptomatic relapse later after drug was stopped.
C.M.	Granular conjunctivitis	Hydrocortisone	8	Improved.
J.M.	Progressive lesions on x-ray film	Hydrocortisone	15	Moderate regression on x-ray film
E.R.	Hilar adenopathy	Hydrocortisone	10	No significant regression
L.S.	Uveitis	ACTH	2	No improvement. (Note—medication voluntarily discontinued after leaving hospital—patient became blind.)
J.C.	Dyspnea Systemic symptoms	Hydrocortisone	6	Marked symptomatic and marked x-ray film improvement

The patients had serial roentgenograms during their period of observation. Based on the last film, the following changes were noted:—(1) no significant change compared to the first film—18 (40 per cent); (2) regression of original lesions—25 (56 per cent); (3) progression with development of superimposed pulmonary tuberculosis—2 (4 per cent).

It is also of interest to record from the radiologic point of view that: (1) the association of a frank pleural effusion with uncomplicated sarcoidosis was seen in only one instance; (2) while regressive parenchymal changes in some instances were quite marked, *unequivocal complete regression* was not noted. Careful review of the x-ray films indicated some infiltration or fibrosis (usually linear in type) as a residue even in the most favorable cases that were followed for many years; (3) development of emphysema (fairly generalized or localized with bulla formation) was not unusual. Spontaneous pneumothorax occurred in one case; (4) in some instances the resultant fibrosis and emphysema was accompanied by lobar contraction and adhesive pleurisy; (5) regressive changes affecting intrathoracic adenopathy generally proceeded at a slower pace than the pulmonary lesions, although in some cases the enlarged nodal shadows apparently reverted to normal. In the three patients who had hilar and/or mediastinal adenopathy without pulmonary lesions, return to a normal x-ray film was noted in one case, regression in one and no change in the other.

It is obvious from the above that depending upon the stage (early or late) in which the patient with sarcoidosis is first seen, the roentgenogram of the chest may simulate other conditions such as, for example, hematogenous miliary or conglomerate nodular tuberculosis, so-called fibroid phthisis with emphysema, beryllosis, pneumoconiosis (particularly silicosis and siderosis), diffuse interstitial fibrosis of the Hamman-Rich type, lymphoma, congestive heart failure, lymphangitic or diffuse nodular carcinomatosis, and fungal disease.

V. *Other Pertinent Laboratory Findings*

In a number of instances frequent repetitive laboratory determinations of various tests were not performed so that some of the findings mentioned below represent an incomplete survey.

(A) *Blood Chemistry:* (1) *serum protein*—20 out of 34 patients (or 59 per cent) had an elevated serum globulin with a normal serum albumin. Hyperglobulinemia is cited frequently as being characteristic of sarcoidosis, particularly in its active phase, but this finding, of course, cannot be considered as diagnostic; (2) *serum calcium*—in 26 cases, 8 (18 per cent) had an abnormal elevation. Hypercalcemia is of greater diagnostic significance since it is not present in most diseases that resemble sarcoidosis. The hypercalcemia may lead to the formation of renal calculi and may eventuate in renal failure.

(B) *The Tuberculin Reaction:* The rather high incidence of negative tuberculin reactors among patients with sarcoidosis has been amply documented for many years. Israel and Sones,[1] for example, in their material noted that two-thirds of the patients did not react to tuberculin, 30 per cent gave positive reactions to second strength PPD and 5 per cent to the first strength. It is interesting that cutaneous anergy

(sometimes called dermal insensitivity) in sarcoidosis is apparently not limited to tuberculin, but extends to the mumps, virus, pertussis agglutinogen, candida albicans extract, tricophyton, and histoplasmin among others. There is dissociation between fixed skin and circulating antibodies.[3] All of the patients in this series had intracutaneous tuberculin tests. Twenty-six (58 per cent) gave a negative reaction to 1:100 OT or second strength PPD.

(C) *The Nickerson Kveim Reaction:* The value of this test as a differential diagnostic tool is still controversial. Siltzbach[3] found positive tests in 85 per cent of his cases with progressive active sarcoidosis. Israel and Sones[1] believe the test lacks diagnostic value. Aside from the interpretative aspects, there are some distinct limitations of the test: (1) it is recommended that for best results, the antigen employed should be obtained from active human sarcoid tissue but this is often difficult to obtain. To the best of our knowledge, the antigen is not commercially available; (2) the antigen made up in hospitals is a rather crude suspension with probable changing specificity and reactivity for each lot. There is no way of determining the potency without human assay on normal patients, patients with known active sarcoidosis and finally patients with other diseases; (3) a biopsy has to be performed at the injection site about four to six weeks after the intracutaneous administration of the antigen. The characteristic positive reaction is the local development of an area of induration which presents the histological appearance of a tuberculoid response resembling sarcoid. Non-specific granulomatous reactions or lesser inflammatory changes should be regarded as negative. Siltzbach stresses that sometimes a positive biopsy may be obtained from the innoculated area even in the absence of definite formation of a papule.

FIGURE 3

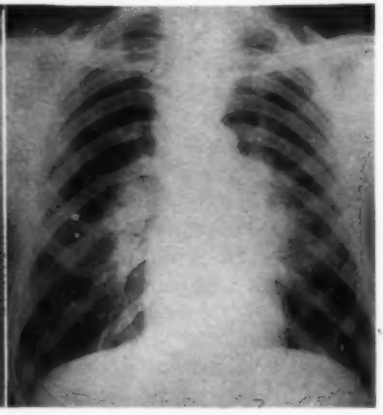

FIGURE 4

FIGURE 3: White man, age 34—x-ray film (June 27, 1950) revealed bilateral predominantly linear infiltration, particularly in lower one-half of both lung fields; cervical node biopsy consistent with sarcoidosis. FIGURE 4: Colored woman, age 31—x-ray film (October 31, 1952) showed bilateral predominantly linear infiltration with adenopathy; cervical node biopsy consistent with sarcoidosis.

In our series, the Nickerson-Kveim test* was performed in 16 patients. A positive histologic test was obtained in four and these had clinical and/or roentgen manifestations of apparently active sarcoidosis. The remaining 12 had negative tests and their disease was apparently inactive at the time; in six of the 12, other biopsy evidence of sarcoidosis had been obtained at an earlier date.

(D) *Pine Pollen Skin Tests:* It is not the intention of the authors to review here the literature regarding the possible etiology of sarcoidosis which is interesting but speculative. Our curiosity, however, was stimulated by Cummings[4] who was impressed with the relatively high incidence of the disease among residents in the forested areas of the United States. He observed that pine pollen extract provoked a delayed type of skin reaction in 50 per cent of his patients.[5] The implication was that sarcoidosis may represent an immunologic response to this pollen. A limited attempt at pine pollen skin testing was undertaken late in the review of our sarcoid cases. The allergenic extract used was pine pollen (scrub pine 50 per cent, yellow pine 50 per cent).** Three dilutions were made so that each 1.0 cc. contained 200, 2000 and 20,000 protein nitrogen units. The following groups of patients received intracutaneously 0.1 cc. of each of the three dilutions and 0.1 cc. of a sterile extracting fluid as a control: (a) sarcoidosis—15 patients with inactive disease; (b) pulmonary tuberculosis—15 with active disease; (c) non-tuberculous chest conditions—15, 13 of whom had carcinoma of the lung; (d) normals—15 doctors and nurses. Readings were made 15 minutes (immediate reaction) and 48 hours after the injection (delayed reaction). An "immediate" positive reaction was defined as the presence of a wheal surrounded by erythema (and usually associated pruritus) in excess of that produced by the control. A "delayed" positive reaction consisted of the appearance of well-defined inflammation, beginning some hours later, and evident 48 hours afterward as a hyperemic indurated area from 1.0 cm. or more in diameter. The readings were classified as negative, slightly positive, moderately positive and markedly positive (necrosis at center of induration). Immediate positive skin reactions with pine pollen (20,000 p.n.u.) were noted in all patients of the groups mentioned; delayed positive reactions were observed with the same dilution in all of the sarcoid cases and in practically every patient in the remaining groups. However, of some interest may be the observation that none of the classes (b), (c), (d) showed delayed positive reactions in dilutions containing 200 and 2000 p.n.u. in contrast to a respective incidence of 30 per cent and 47 per cent positivereactions among the sarcoid patients. It is realized, of course, that the total number of individuals tested is small and no attempt is being made to draw conclusions, but perhaps further investigation is merited.

VI. *Course and Prognosis*

From a chest x-ray film point of view, as mentioned earlier, 56 per cent showed regression of their disease, 40 per cent showed no change and two

*The antigen was obtained through the courtesy of Dr. Louis Siltzbach, Mt. Sinai Hospital, New York City.

**Made by Hollister-Stier Laboratories, Philadelphia, Pa. Appreciation is expressed to Dr. Rubin Grossman, Assistant Attending Physician, for this phase of the study.

(4 per cent) developed super-imposed pulmonary tuberculosis with positive sputum. Two who showed regressive chest x-ray film changes revealed subsequent evidence of extra-pulmonary tuberculosis, particularly of the osseous system. This made a total incidence of four (9 per cent) cases of tuberculosis. A total of five (11 per cent) had electrocardiographic changes compatible with chronic cor pulmonale.

(A) *Living:* Forty of the 45 cases (89 per cent) are living. Sixteen (40 per cent) have been followed for less than five years and 24 (60 per cent) for more than five years, the longest being 18 years. Thirty-seven (93 per cent) are working or able to work. The remaining three (7 per cent) are unable to work because of marked dyspnea in one, blindness due to uveitis in another and disabling rheumatoid arthritis in the third. One patient with superimposed pulmonary tuberculosis (admitted about seven years after the diagnosis of sarcoidosis was made) received appropriate chemotherapy and now has inactive disease. Another patient developed tuberculosis of the sternum and spine (about two years after the diagnosis of sarcoidosis was made). A fusion operation was done for the latter and at the time of the procedure, the culture from the associated cold abscess was positive for tubercle bacilli. She also received chemotherapy and the disease is inactive.

(B) *Died:* Five of the 45 cases (11 per cent) died. Their length of survival ranged from two to nine years. Two (40 per cent) died of respiratory insufficiency, chronic cor pulmonale and right heart failure. Two (40 per cent) died of tuberculosis. The diagnosis of sarcoidosis in one of them was made in 1943 (positive x-ray film findings and negative tuberculin test); fibrosis and emphysema developed and in 1948, spontaneous pneumothorax (right) occurred. Several months later, six deep x-ray treatments for sarcoidosis were administered in another institution. A florid type of tuberculosis ensued and streptomycin and PAS were of no avail. She also developed right heart failure and died at the Pollak Hos-

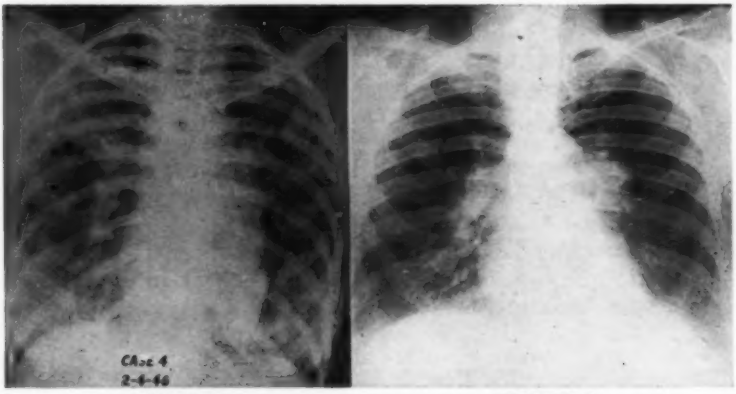

FIGURE 5 FIGURE 6

FIGURE 5: Colored woman, age 27—x-ray film (February 4, 1946) showed diffuse mixed type of infiltration with some confluence and adhesive mediastinal pleurisy; plaque-like erythematous skin lesions on legs biopsied and consistent with sarcoidosis.
FIGURE 6: White woman, age 43—x-ray film (October 5, 1953) showed bilateral hilar adenopathy but no parenchymal involvement. Lesion has remained unchanged. No biopsy confirmation. Had history of parotid gland enlargement which receded spontaneously.

pital in April, 1949. Another aptient had clinical and roentgen findings compatible with sarcoidosis which was confirmed by biopsy. Subsequently he developed multiple cold abscesses (from which tubercle bacilli were isolated) associated with bony changes. This patient died before the era of chemotherapy for tuberculosis. Autopsies were obtained in both of these patients. The fifth died at home (nine years after a diagnosis of sarcoidosis was made) but the cause is not known.

VII. *Treatment*

The agents that have been used in the past in the therapy of sarcoidosis have been many and ineffective. The advent of ACTH and cortisone, however, has provided drugs which may produce some suppressive effect in some instances.

The efficacy of steroids is variable, being more apparent in some organs and tissues than others, and more dramatic in symptomatic patients particularly in the early stages of the disease. There appears to be general agreement that hormonal therapy is indicated in sarcoidosis for: (a) eye lesions—to avoid blindness; (b) suspected myocardial involvement; (c) hepato-splenomegaly; (d) persistent hypercalcemia—because of the prospect of formation of calculi with renal failure; (e) possible symptomatic improvement of dyspnea in the late stages when this symptom is due to fibrosis and/or emphysema; (f) disfiguring skin lesions—topical application may be tried first; (g) progressive chest x-ray film changes, especially in the symptomatic patient.

It has been noted that intrathoracic lymphadenopathy generally responds poorly or not at all to steroids.

Short courses of steroids are generally desirable, but the duration of therapy should be determined by the indication for its use and the character of the response obtained. One must be extremely careful to make sure that there is not underlying or associated tuberculosis. Close observation with frequent sputum and roentgen examinations is important. It is wise to add antituberculosis drugs as a preventive measure.

Table I lists the primary indication, the agent used, the length of treatment and the result obtained in the eight patients who received steroids. All but two showed improvement during this therapy. No complication was noted. One (L.K.) had a symptomatic relapse after hydrocortisone was stopped.

SUMMARY

In a review of clinical material, 45 cases have been accepted for inclusion in a study of sarcoidosis. Twenty (44 per cent) had histologic confirmation and in the remainder, prolonged observation on the basis of clinical, roentgenological and laboratory findings made the diagnosis tenable. Forty (89 per cent) are living and all but three are working or able to work. Sixty per cent of the living cases have been followed for at least five years, the longest 18 years. Five (11 per cent) died and their length of survival ranged from two to nine years. The causes of death were: (a) chronic cor pulmonale and right heart failure (40 per cent); (b) tuberculosis (40 per cent) (c) cause unknown (20 per cent).

Comparing the first and last x-ray film of each patient, it was observed that: (a) regression occurred in 56 per cent; (b) no significant change in 40 per cent; (c) progression with development of super-imposed tuberculosis (positive sputum) occurred in 4 per cent.

Prognosis is good for the majority of patients with sarcoidosis. The rate of spontaneous regression of thoracic lesions is favorable. There is no specific treatment, but steroids may exert a suppressive effect in some instances. Eight patients (18 per cent) in this series received steroids. All but two showed improvement during therapy and one had a symptomatic relapse after its cessation.

RESUMEN

Se incluyeron 45 casos en un estudio de material clinico de sarcoidosis. Viente (44 por ciento) estaban confirmados histológicamente y el resto tenían diagnóstico basado en la observación prolongada tanto clínica como radiológica y con hallazgos de laboratorio. Cuarenta (89 por ciento) viven y con excepción de tres, todos estan capacitados para trabajar. Sesenta por ciento de los que viven, se han observado por lo menos durante 5 años y el que mas tiempo se ha seguido, ha llegado a 18 años de observación. Cinco (11 por ciento) murieron y el tiempo de su sobrevida varió desde dos a nueve años.

Las causas de la muerte fueron: (a) cor pulmonale crónico e insuficiencia cardiaca derecha (40 por ciento); (b) tuberculosis (40 por ciento); (c) causa desconocida (20 por ciento).

Comparando la primera y la última radiografía de cada enfermo se observó que: (a) hubo regresión en 56 por ciento; (b) no hubo cambio de importancia en 40 por ciento; (c) marcha progresiva con desarrollo de tuberculosis agregada (esputo positivo) en 4 por ciento.

El pronóstico es bueno para la mayoría de los enfermos de sarcoidosis. La proporción de regresión espontánea de lesiones torácicas es favorable. No hay tratamiento específico, pero los esteroides pueden ejercer un efecto regresivo en ciertos casos. Ocho enfermos (18 por ciento) de esta serie se trataron con esteroides. Con escepción de dos, los demas mejoraron durante el tratamiento y uno tuvo recaída después de cesar ese tratamiento.

RESUMÉ

Dans une revue de cas cliniques, 45 observations ont été acceptées pour figurer dans une étude sur la sarcoïdose. 20 (44%) reçurent une confirmation histologique, et pour les autres, une observation sur la base de constatations cliniques, radiologiques et bactériologiques rendit le diagnostic soutenable. 40 cas (89%) sont en vie et tous sauf trois travaillent ou sont en état de le faire. 60% des malades en vie ont été suivis pendant au moins cinq ans, et pendant 18 ans pour la plus longue période. Cinq malades (11%) moururent et leur période de survie atteignit de deux à neuf ans. Les causes de la mort furent: (a) coeur pulmonaire chronique et atteinte du coeur droit (40%); (b) tuberculose (40%); (c) cause indéterminée (20%).

En comparant le premier et le dernier cliché de chaque malade, on observa que: (a)une régression survint dans 56% des cas; (b) il n'y eut pas de modification nette dans 40%; (c) la progression avec extension d'une tuberculose surajoutée (expectoration positive) survint dans 4%.

Le pronostic est bon pour la grande majorité des malades atteints de sarcoïdose. Le taux de régression spontanée des lésions thoraciques est favorable. Il n'y a pas de traitement spécifique, mais les corticostéroïdes peuvent amener un effet régressif dans quelques exemples. 8 malades (18%) dans ce groupe reçurent des corticoïdes. Tous sauf deux montrèrent une amélioration pendant le traitement et l'un d'entre eux fit une rechute après sa cessation.

ZUSAMMENFASSUNG

Bei einer Durchsicht unseres klinischen Materials erwiesen sich 45 Fälle als geeignet zur Aufnahme in eine Untersuchung über Sarkoidose. Bei 20 (44%) lag eine histologische Bestätigung vor, während bei den übrigen eine längere Beobachtung auf der Grundlage klinischer, röntgenologischer und Laboratoriumsbefunde die Diagnose wahrschleinlich machte. 40 (89%) leben, und alle-bis auf 3-arbeiten oder sind arbeitsfähig. 60% der am Leben befindlichen Fälle wurden mindestens 5 Jahre nachbeobachtet, der längste 18 Jahre. 5 (11%) starben, wobei die Länge der Überlebenszeit zwischen 2 und 9 Jahren betrug. Die Todesursachen waren: (a) chronisches cor pulmonale und Versagen des rechten Herzens (40%); (b) Tuberkulose (40%), (c) unbekannte Ursache (20%).

Bei einem Vergleich des ersten und des letzten Röntgenfilmes jedes Kranken beobachtete man, daß: (a) eine Rückbildung in 56% eintrat; (b) keine wesentliche Veränderung in 40%; (c) eine Progredienz mit Entwicklung einer aufgepfropften Tuberkulose (positives Sputum) trat in 4% ein.

Die Prognose ist günstig für die Mehrheit von Kranken mit Sarkoidose. Die Ziffer von spontanen Rückbildungen thorakaler Veränderungen ist günstig. Es gibt keine spezifische Behandlung; immerhin können in manchen Fällen Steroide eine hemmende Wirkung ausüben. 8 Kranke unserer Reihe (18%) erhielten Steroide. Sie zeigten allemit 2 Ausnahmen-eine Besserung während der Behandlung; ein Kranker hatte einen symptomatischen Rückfall nach beendeter Behandlung.

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Bilateral Primary Invasive Carcinoma of the Lungs

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The multicentric origin of certain neoplasms such as those of the stomach, intestines, skin, female genitalia, and pharynx have been well documented.[1,2] Until recently, this phenomenon has not been emphasized for carcinoma of the lung except in those examples designated as alveolar cell carcinoma. Excluding the latter, there have been 26 documented cases of multiple primary invasive carcinoma of the lungs with 15 of these appearing in the American literature. McGrath *et al.*[3] and Auerbach *et al.*[4] each noted five cases containing two primary invasive bronchogenic carcinomas in the same or different lobe during their independent study of bronchogenic carcinoma, but the histologic types and locations of these carcinomas were not presented. However, the authors were primarily interested in noting all neoplastic change throughout the bronchial mucosa of lungs already known to contain bronchogenic carcinoma. The association of carcinoma *in situ* in one lung with invasive carcinoma in the same or contralateral lung has similarly received recent attention.[5-7]

The purpose of this report is to present another example of multiple primary invasive carcinomas of the lung and to tabulate the previously reported examples.

This 82 year-old white man was admitted to the Veterans Administration Hospital, Pittsburgh, for repair of a right inguinal hernia. During previous admissions, he had a transurethral resection of the prostate for benign prostatic enlargement and a mid-thigh amputation of the left leg for arteriosclerosis obliterans.

His only complaint on readmission was dry, non-productive cough of several years duration. A routine chest x-ray film revealed an area of increased density about the left hilum extending into the lung and a patchy ill-defined density in the middle of the lower lobe of the right lung.

FIGURE 1: Posterior view of lungs revealing neoplastic mass in superior mediastinum. The tumor evident here histologically was of undifferentiated "oat cell" type.

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Bronchoscopic examination revealed no intraluminal growth and no biopsy was obtained. The bronchial secretions and sputum examinations were negative for neoplastic cells and acid-fast bacilli on smear and culture. A biopsy of a left scalene node revealed chronic lymphadenitis.

Subsequent x-ray examination of the chest revealed enlargement of the two masses as noted previously. Because these radiographic changes were highly suspicious of extensive carcinoma of the lung, x-ray therapy was initiated. He received a total of 5200 r to his left chest and 3200 r to the right, over a two month period. The left hilar mass decreased in size, but the lesion of the right lung appeared larger.

He deteriorated rapidly and died five months after admission.

Autopsy Examination

At necropsy, the lungs were partially bound to the thoracic wall by fibrous adhesions and there was bilateral hydrothorax. The superior mediastinum was encased in gray, firm tumor tissue (Fig. 1). The pleural surfaces of the left lung and the pericardium were studded by firm white nodules averaging 0.5 cm. in diameter. The remaining pleural surfaces were bluish gray, smooth and glistening. The cut surfaces of the lungs revealed a gray, firm, demarcated, circumscribed mass of neoplastic tissue averaging 2.0 cm. in diameter located in the middle and lower lobe of the right lung (Fig. 2). The remaining parenchymal surfaces were grayish-pink to black except in the left anterior hilar region where the gray mediastinal tumor infiltrated the adjacent parenchyma. The bronchial mucosa of the left main stem bronchus was red and granular. Metastases were noted in the brain, skin, pancreas, adrenals, bone marrow, and hilar and abdominal lymph nodes.

Additional findings were severe generalized atherosclerosis with arteriosclerosis obliterans of the left iliac artery and a small infarct of the upper lobe of the left lung.

Microscopic examination revealed two distinct histologic types of carcinoma of the lung. The larger tumor present in the left lung was comprised of round, oval, and spindle shaped anaplastic basophilic cells arranged in large sheets and smaller nests. Cell nuclei were oval, hyperchromatic and frequently exhibited mitotic forms (Fig. 3). One section revealed the tumor in continuity with the epithelial surface of an upper lobe bronchus particularly the reserve cell layer. Adjacent mucosal epithelium revealed moderate dysplasia. A considerable amount of desmoplastic tumor stroma was present throughout the neoplasm. This morphologic appearance was apparent in all metastatic sites which included the brain, skin, pancreas, thyroid, adrenals, bone marrow, hilar and abdominal lymph nodes, mediastinum and pleurae.

The other neoplasm which was in the right lung arose from a bronchial epithelium which had undergone squamous metaplasia. It was composed of irregular sheets and whorls of differentiated squamous epithelial cells with acidophilic cytoplasm and varying sized hyperchromatic nuclei some of which contained mitotic forms (Fig. 4).

FIGURE 2: Anterior view of right lung revealing squamous cell carcinoma.

Discussion

The identification of multiple primary invasive carcinomas of the lung may be attendant with difficulty. It is apparent that pulmonary metastases from an ipsilateral or contralateral primary pulmonary neoplasm may at times provoke such a diagnostic problem. Analysis of previously reported cases,[4-20,23] as well as that presented herein allow for certain criteria which permit such a diagnosis.

The microscopic demonstration of an invasive carcinoma arising from an area of carcinoma *in situ* or adjacent dysplastic epithelium at two distinct bronchial sites would appear to represent absolute diagnostic features for multiple primary bronchogenic carcinomas. Since the local tumor growth may destroy the area of *in situ* change, the presence of two or more distinct cellular types of bronchogenic carcinoma may be considered acceptable. Examples in which one neoplasm represents an undifferentiated polymorphous large cell type and the other a squamous cell carcinoma do not appear acceptable unless their mucosal origins can be clearly visualized histologically since the former may actually represent anaplastic change of the squamous variant. It is obvious that extrapulmonary carcinomas may give rise to pulmonary metastases simulating primary bronchogenic carcinomas. Examples of pulmonary neoplasms morphologically resembling other extrapulmonary tumors should not be included as examples of multiple bronchogenic carcinomas. Extreme caution in this regard is necessary since an occasional pulmonary metastasis may erode into bronchi and thus simulate a primary mucosal tumor.

The case presented fulfills the criteria noted above. It is of interest that despite the anaplastic small cell nature of one of the growths dysplastic mucosal change was evident. It is noteworthy that this type of bronchogenic carcinoma rarely allows for the clear demonstration of its derivation from the surface epithelium of the bronchial mucosa as indictaed by Williams.[7] Further, the metastatic deposits were all of the anaplastic variety being morphologically identical to the tumor of the left lung. It would be highly unlikely that the more differentiated squamous cell carcinoma metastasized to the opposite lung and other visceral sites as an extremely anaplastic form. Conversely, it is unlikely that the latter metastasized to the other lung as a well differentiated squamous cell carcinoma. Although Simpson[21] in 1929 indicated that squamous cell carcinoma may metastasize as an oat cell variety, more recent experience with pulmonary carcinoma contradicts such a statement. McGrath, *et al.*[3] have indicated from their meticulous study that mixed histologic patterns were produced by independent growths which subsequently coalesce. It is highly conceivable that the primary tumor described by Simpson may have been a mixed histologic pattern with only the oat cell exhibiting metastases, since it has been shown that the mixed morphologic tumors become more frequent with increased sampling of the lesions.[2,22] Numerous microscopic sections of our tumors failed to reveal a mixed pattern.

The paucity of reported cases of multiple primary invasive pulmonary carcinoma suggests that such an event is rare. However, attention to the association of invasive bronchogenic carcinoma with multiple areas of carcinoma *in situ* within the bronchial mucosa would indicate the multicentric potential of pulmonary tissue for neoplastic growth.[3-6,12]

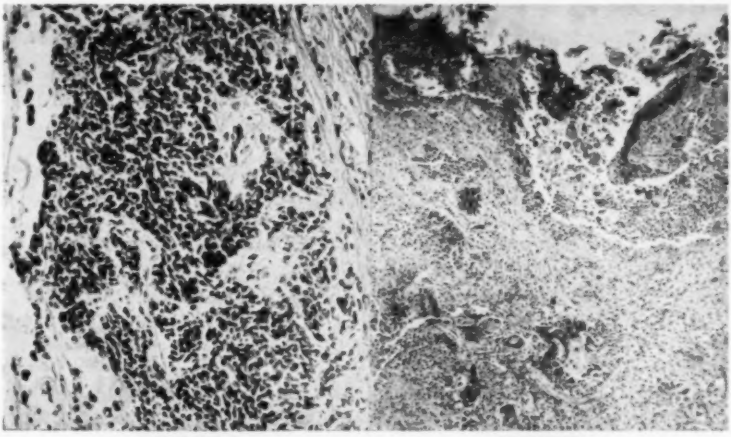

FIGURE 3 FIGURE 4

FIGURE 3: Photomicrograph of classical undifferentiated, "oat cell" carcinoma in left lung. (X 230) FIGURE 4: Photomicrograph of apparent site of origin of squamous cell carcinoma of right lung. Severe squamous metaplasia and dysplasia is subtended by invasive squamous cell carcinoma. (X 120)

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SUBLINGUAL ADMINISTRATION OF TRYPSIN IN CHRONIC BRONCHITIS

Thirteen patients with chronic bronchitis and pulmonary tuberculosis have been treated with trypsin given sublingually.

A decrease of cough, together with more effective expectoration, has been noted.

Pulmonary function tests demonstrate an improvement of the respiratory efficiency, with increase of the vital capacity, maximum breathing capacity, CO_2 removal, air velocity index and decrease of the dead space.

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Aspergillosis of the Lung

NEWELL T. BRAATELIEN, M.D.,* and HAROLD M. PERLMUTTER, M.D., F.C.C.P.
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Virchow, in 1856, found aspergillosis infection in patients dying of other diseases. Bussler, in 1887, reported a case of a woman, who for 11 years coughed up dark bodies the size of a pea, which consisted almost entirely of the mycelia and spores of the aspergillus. It has been reported as an occupational disease in people handling grains.

We desire to present the following three cases:

Case 1 is that of a 35 year-old white woman whose work on a farm included the cleaning of a grain storage building where she was exposed to heavy concentrations of grain dust. She consulted her physician because of hemoptysis, weight loss and night sweats. She gave no history of tuberculosis contact. X-ray films taken at that time showed a soft infiltration within which was a small cavity in the upper lobe of the right lung. She was admitted to the tuberculosis sanatorium where Mantoux, smears and coccidioidin skin tests were negative. Her x-ray films at the sanatorium (Fig. 1) again showed an infiltrative lesion with small cavities occupying the apical segment of the upper lobe of the right lung. Bronchoscopy and bronchial washings gave no further information.

Laboratory studies including blood count and sedimentation rate were relatively normal.

She continued to have bouts of hemoptysis. Repeat x-ray films showed no regression of the lesion. Exploratory thoracotomy revealed the apical and posterior segments to be involved in a firm nodular mass with areas of scarring atelectasis. These segments were removed. She had had an uneventful postoperative course.

Pathological study revealed a fibrous adhesion measuring 9 x 11 x 13 mms. on the pleural surface. Dissection of the bronchi revealed a cavity closely adjacent to the proximal portion which measured 3 x 2 x 2 cms. The lumen contained friable grayish brown material. The wall of the cavitay was composed of dense grayish-white tissue which varied from 1 to 3 mms. in thickness.

The friable grayish-brown material in the cavity contained numerous mycelial threads. The inner surface was lined by chronic inflammatory granulation tissue. The wall of the cavity was thick and composed of fibrocytes and many lymphocytes. The lymphocytes formed many follicles without secondary centers. The adjacent lung parenchyma was fibrotic. The alveolar spaces were collapsed and contained histiocytes with brown pigment.

Culture on Sabouraud's media grew large numbers of mycelial threads, a few of which showed conidiophores with bulbous ends. The large number of colonies indicated the organism had the characteristics of the genus *Aspergillus fumigatus*.

Two years after surgery, she is well.

Case 2 is that of a 35 year-old white man who was exposed to large concentrations of grain dust.

His presenting complaints consisted of cough and chest pain. The initial x-ray films taken by his family physician demonstrated a large cystic structure in the upper lobe of his right lung. Shortly thereafter, he developed fever with increase in cough. He was placed on antibiotics and improved clinically. Repeat x-ray film (Fig. 2) demonstrated a thick walled abscess 7 cm. in diameter with a fluid level present. Laboratory studies showed only slightly elevated sedimentation rate. The Mantoux tuberculin test was negative. Sputum studies and bronchial washings were negative for specific organisms. Bronchoscopy gave no further information.

At thoracotomy, the upper lobe of the right lung was firm and a large cavity occupied its greatest portion. The entire right upper lobe was excised and he recovered uneventfully from surgery.

Pathological study showed the pleural surface of the specimen to be thickened and covered with grayish fibrous adhesions. On opening the bronchus to the posterior segment, a large cavity was entered which was filled with reddish-brown serous fluid and granular material. The smaller bronchi in this area contained plugs of soft gray material which were cylindrical and were from 0.5 to 1.0 cms. long. The abscess measured 6.9 x 5.6 cms. The wall of the cavity was thickened, the lining was grayish-brown and shaggy. The remainder of the lung substance was collapsed.

*Pathologist, Moline Public Hospital.

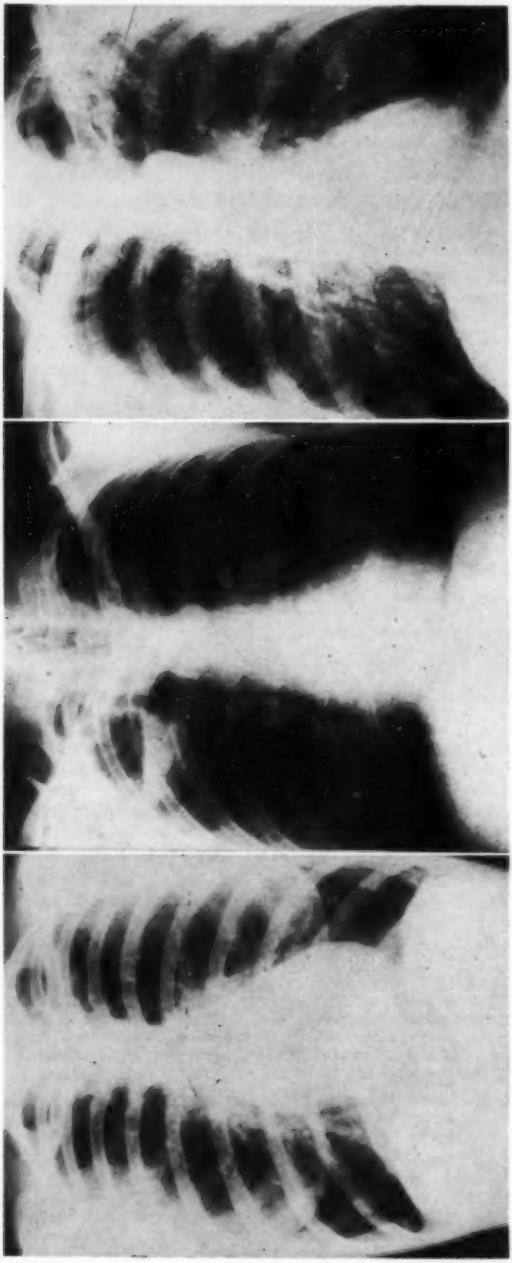

FIGURE 3

FIGURE 2

FIGURE 1

The sections of the abscess wall contained fibrous tissue which was heavily infiltrated with lymphocytes, plasma cells, and large numbers of eosinophiles. The lumen of the abscess contained large amounts of nuclear debris and eosinophiles, neutrophils, and erythrocytes. In a few areas, structures were present which appeared to be septate branching hyphae which had formed terminal spores.

The sections of the remainder of the lung contained scattered foci of necrosis surrounded by fibrous tissue. The alveolar walls were thickened and infiltrated with lymphocytes, and the alveoli contained numerous mononuclear phagocytes. The plugs of material from the bronchi were made up of masses of hyphae. Cultures of these established the diagnosis of aspergillosis.

Now, over a year since surgery, he still has a cough. On iodine administration, he has shown some improvement. His prognosis is questionable.

Case 3 is that of a 47 year-old office worker. He gave no history of environmental contacts relative to his pathology.

He was seen by his physician with a three-month history of progressive asthenia, weight loss, night sweats and only minimal coughing. He was hospitalized with a temperature of 101°F. His red cell count was 5,020,000; white cell count 9,800; hemoglobin 99 and sedimentation rate of 70 mm.

The initial x-ray film (Fig. 3) revealed evidence of demonstrated bilateral emphysema with an inflammatory process in the upper lobe of the left lung. There was an irregular area of confluent infiltrates, which produced a heterogenous area of increased densities and small areas of decreased density. Several sputum specimens showed only gram positive and gram negative bacilli and few mycelial elements. Sensitivity studies were carried out for the organisms present and appropriate antibiotics given.

Bronchoscopy and washings added no information. The Mantoux tuberculin test, coccidioidin and histoplasmin tests were negative.

Laminography 10 days after the initial x-ray film showed some narrowing of the peripheral portions of the apical segmental bronchus. There was retraction of the hilum upward. Several small cavities were visualized surrounded by areas of fibrosis.

The left upper lobe was excised and he made an uneventful post-operative recovery and has remained well.

The apex and the posterior apical portion were covered by reddish-gray fibrous tissue. On opening the major bronchi to the region of the apex, several cysts and areas of firm consolidation were encountered. Some of the cysts contained yellowish-gray mucopurulent material and at the apex of the lung, a single large cavity was present. The cavity measured up to 2 centimeters in diameter. No definite communication with the bronchus and this cavity could be found.

Microscopic examination showed extensive chronic inflammation and fibrosis throughout all portions of the sections. Small isolated bronchioles were present, some of which were collapsed, others dilated and contained either inflammatory cells or cellular debris. Scattered throughout the tissue were large numbers of lymphocytes and plasma cells and varying numbers of pigmented phagocytes together with large fibroblasts and mononuclear cells. In some areas, abscess cavities were present and were lined either by chronic granulation tissue or by columnar epithelium. In one of the sections, a mass of foreign material was present which was surrounded by neutrophis. This was made up of numerous interlacing and apparently septate mycelia. These were tightly packed and lying between them were scattered erythrocytes. Cultures from the abscess cavity grew a fungus identified as *Aspergillus fumigata*.

Discussion

The role of the aspergillus, whether a primary or secondary invader, is difficult to determine. Aspergilli have been found associated with other primary lung pathology. It has been isolated from sputum of patients with asthma, tuberculosis, infarction, bronchiectasis and carcinoma.

In our first two cases, the exposure to grain dust and the pathological findings substantiate a diagnosis of primary aspergillosis. In the second case, there was no demonstrable invasion of the abscess wall by the aspergillus. Henchman, Moore and Plummer[1] state that a histologic response is not mandatory for a diagnosis. The diagnosis may be based on finding circumscribed plugs which come from the bronchi. These plugs consist of mycelia bound together by fibrin.

Our third case gave no history relevant to a diagnosis of aspergillosis. This case may well demonstrate bronchopneumonia which clinically has been abated by antibiotics leaving the secondary invading mycelia to continue as a primary pathogen. The increasing incidence of fungus infections following the use of antibiotics is well known.

The clinical diagnosis of aspergillosis is difficult. Schneider[2] feels that this condition is being overlooked because of its close resemblance to tuberculosis. He states that animals inoculated with spores from a pure culture of *Aspergillus fumigatus* presented autopsy findings typical of tuberculosis. Aspergillosis infection in man starts insiduously with a loss of strength, anorexia, night sweats and evening temperature. Hemoptysis is frequent.

The finidnig of *Aspergillus fumigatus* in the sputum is not sufficient to make the diagnosis. Only if all other diagnostic measures have been exhausted in finding an etiologic agent should a tentative diagnosis of aspergillus be made.[3] The aspergillus may be a secondary invader in such acute conditions as bronchopneumonia and when the latter has responded to drugs, the aspergillus may take over as the primary pathogen. A review of our cases of unresolved pneumonia may result in a higher incidence of aspergillus involvement of the lung.

The medical therapy of aspergillosis of the lung is primarily supportive with some benefits provided by iodides.[3]

Surgical intervention of localized lesions should provide an effective measure in treatment.[4] Several cases have been reported of localized lesions in which segmental resections were carried out with favorable results. Hochberg, Griffen and Bicunas[5] also report a case of localized aspergillosis treated successfully by surgery.

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A TECHNIQUE FOR TRANSEPTAL LEFT HEART CATHETERIZATION VIA THE RIGHT EXTERNAL JUGULAR VEIN

Transeptal catheterization of the left atrium can be performed without serious complications. To enable leg exercise during the left heart catheterization, we have used the transeptal puncture technique through the right external jugular vein.

The ability to pass the catheter from the left atrium to the ventricle is dependent on the anatomical conditions. In the case of a marked mitral stenosis combined with a sharp regurgitant jet and a very large left atrium, it may obviously be difficult to pass a thin polyethylene tube through the orifice. The chance might be better with the stiffer teflon catheter moved under the control of screening. Passing the catheter from the superior vena cava to the right atrium the direction is straight against the mitral orifice.

The procedure is not harmful for the patient. The metal tube may occasionally cause some pain in the region of the right shoulder. After removal of the metal tube when only the catheter remains in the vein, this discomfort disappears. The catheter can remain within the left side of the heart for the time needed to get the patient into a steady state for estimation of cardiac output and pressures both at rest and during exercise. The "basic" condition of the patient was not disturbed by the procedure. There is no risk of air embolism from the incision in the jugular vein, as the head is not elevated and the veins are distended with blood when the instrument is introduced.

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Massive Pulmonary Infarction Simulating Carcinoma of the Lung*

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Many inflammatory and other benign lesions of the lung may imitate carcinoma of the lung, both clinically and radiologically. Often thoracotomy, and even pulmonary resection, is necessary to rule out the presence of a malignant lesion. One of the rarer lesions that has been mistaken for carcinoma of the lung is a localized infarct of the lung. Neville and Munz[1] have reported two cases in which a segmental resection and a lobectomy were performed respectively for lung infarcts thought to be carcinoma grossly. Perkins and Bradshaw[2] also cite two cases in which limited pulmonary resections were performed for localized lesions that were later found to be infarcts of the lung. A similar case has been reported by Smith.[3] In such cases as these, resection was deemed necessary only to rule out a more serious pathologic entity, for localized infarcts of the lung can be expected to heal spontaneously.

We are unaware, however, of any reported case in which a massive infarct simulated carcinoma of the lung clinically. We wish to report such a case which was treated successfully by lobectomy.

Case Report

D. F., a 51 year-old portrait painter, entered Stanford University Hospital with a history of a five-week illness beginning with coryza, sore throat, and cough, accompanied by fever ranging between 100°F and 103°F. Two weeks after the onset of this illness, he experienced a sharp pain in his right anterior chest and transient aching in his left calf. In spite of antibiotics, the fever continued, and a chest film demonstrated right pleural effusion. Bronchoscopy and right thoracentesis had been performed at another hospital where 650 cc. of serosanguineous pleural fluid had been

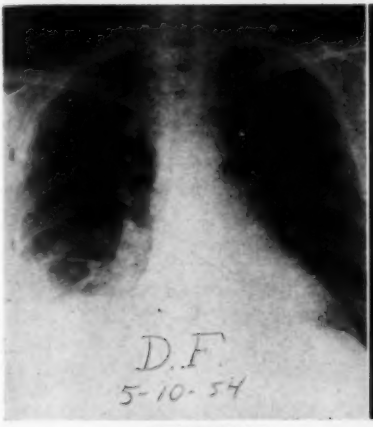

FIGURE 1A

FIGURE 1B

FIGURE 1A: Preoperative posteroanterior chest film showing right pleural effusion and density of right lower lobe. FIGURE 1B: Preoperative lateral chest film showing extent of density in right lower lobe.

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obtained, while bronchoscopy revealed no abnormality. No tumor cells or acid-fast bacilli were found in this effusion. A culture of the pleural effusion grew out Streptococcus fecalis. On the basis of the appearance of the chest films (Fig. 1) and the serosanguineous nature of the effusion, the referring physician felt that the most likely diagnosis was carcinoma of the lung with pleural metastases.

On admission to our hospital, physical examination revealed the following: temperature 100° F., pulse 90, and blood pressure 120/74 mm.Hg. Abnormal findings were limited to the right hemithorax, where a respiratory lag was noted. There was dullness to percussion at the right base posteriorly, with coarse rales and a friction rub. The legs were not swollen and there were no areas of tenderness. Hematocrit was 43, and the white cell count was 13,800 with 81 segmented polys. The tuberculin test was positive and the histoplasmin and coccidioidin skin tests were negative. The serology was negative.

Four days after entry his temperature rose to 102°F. and the rales in the right lung increased. The white cell count was 18,000 with 86 polys.

The x-ray film appearance of collapse of the right lower lobe, the bloody pleural effusion, and the recurrent pneumonitis suggested to us also that the most likely diagnosis was carcinoma of the lung with extension to the pleura. Thoracotomy was advised to obtain a tissue diagnosis.

One week after admission, thoracotomy was performed through the bed of the fifth rib. Heavy, fibrous pleural adhesions were noted, especially around the lower lobe. One thousand cc. of yellowish, serosanguineous fluid were removed. The lobes were separated and it was noted that the lower lobe was uniformly firm and liver-like in consistency. Frozen section of an area of thickened pleura was reported as "chronic inflammation." Several hilar nodes were enlarged and appeared inflammatory. The lower lobe appeared to be diseased, and therefore lobectomy was performed. As the main lobar artery was divided, it was found to be completely occluded by a thrombus.

The pathologist's report was as follows: "Gross specimen: greatly thickened pleura. The most striking feature is the complete occlusion of the main artery of the lobe by thrombus; the bronchi are clear. Most of the lobe feels diffusely more firm than normal. Histological examination: the pulmonary artery to this lobe is completely occluded by a fairly recent thrombus which shows only beginning fibrosis at its perphery. The lung parenchyma is necrosed over large areas. In others, there is partial to almost complete collapse with macrophages in most of the alveoli. The pleura is thickened with fibrosis and heavily infiltrated with acute inflammatory cells. On its surface are thick strands of fibrin. Diagnosis: embolism, pulmonary artery, (right lower lobe); infarct, lung (right lower lobe); collapse, lung (right lower lobe)." Cultures of the pleural fluid were sterile. Cultures of the lung tissue grew only a few Staphylococcus albus; there was no growth of fungi or tubercle bacilli.

Following surgery a gradual decrease in his fever occurred. On the eighth postoperative day, he developed thrombophlebitis in the calf. This responded to conservative measures and he was discharged home on the 13th postoperative day (Fig. 2).

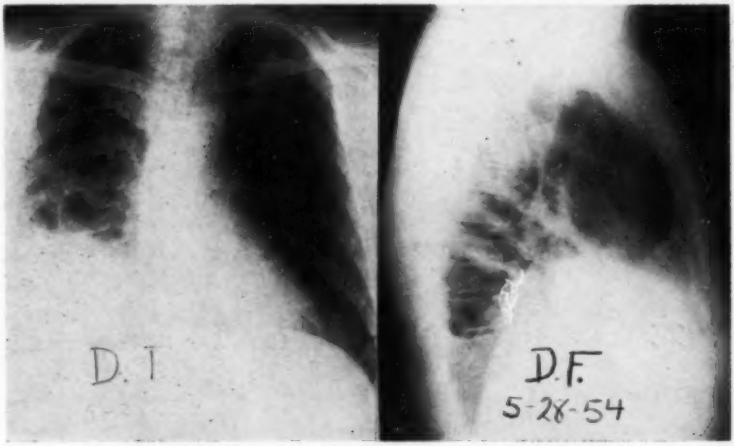

FIGURE 2A FIGURE2B

FIGURE 2A: Postoperative chest film showing expansion of remaining right lung and small amount of residual fluid. FIGURE 2B: Postoperative lateral film. Note the absence of the previous posterior density.

Three weeks later he was readmitted with recurrent thrombophlebitis in the left leg. Again he was treated conservatively for 10 days, and was discharged as improved. During the next month he was seen in the outpatient clinic, when it was felt that he had recurrent thrombophlebitis. A program of rest, elevation, and support was advised. Subsequently, he was in good health until 18 months later when he committed suicide for causes unrelated to his previous illness.

Discussion

The disregarded history of transient aching in the calf previous to the pleuritic pain, and the protracted and recurrent thrombophlebitis postoperatively make it extremely likely that the leg veins were the source of the embolus. This is in keeping with reports of large series of pulmonary emboli, stating that the veins of the lower extremities are the source of the emboli in from 83[4] to 86[5] per cent.

It has been shown both experimentally[6-9] and clinically[10] that pulmonary embolism in an otherwise healthy lung does not produce an infarct. This has been explained as a result of the complex interrelationship of the three pulmonary vascular systems, namely the pulmonary arteries, the bronchial arteries, and pulmonary veins. Mathes and her co-workers[6] feel that the bronchial arteries in an otherwise healthy lung can nourish pulmonary vasculature beyond an embolus through capillary anastomoses. Ellis *et al.*,[7] however, concluded that the pulmonary artery itself was capable of supplying blood to an area distal to an embolus by capillary anastomoses. This was true, however, only if some part of the pulmonary artery supply to a lobe remained. If emboli were present in each branch of a given lobe, then there was no possible way for unoxygenated blood to go around the block. The case reported by Woesner *et al.*[10] of thrombi occluding the pulmonary arteries to the middle and lower lobes without infarction supports the idea that the bronchial arteries alone can nourish large areas of pulmonary tissue. Ligation of the main pulmonary artery did lead to massive infarction in one reported case, but the author postulated that early onset of infection in the lung was a predisposing factor.[11]

In the absence of heart failure, the factors which predispose to pulmonary infarction are pleural effusion, bronchial obstruction, atelectasis, pneumonia, multiple emboli, and shock.[12] Parin[13] states that the sudden occlusion of a portion of the pulmonary vascular tree may cause peripheral hypotension by a reflex mechanism, and in turn, decrease the bronchial circulation. However, the experimental studies of Hara and Smith[14] have not confirmed this.

One might ask why infarction occurred in our patient. The size of the embolus, occluding all of the pulmonary arterial blood to the right lower lobe would be sufficient explanation if one agreed with Ellis[7] that the bronchial arteries were probably of little or no importance in the etiology. On the other hand, this does not explain Woesner's case where two lobes were apparently nourished satisfactorily by the bronchial arteries. It has been stated that pleural effusion may predispose to infarction by interference with pulmonary venous drainage. However, pleural effusion often follows infarction, and this was probably the sequence in this case. Bronchial obstruction and atelectasis were not present and thus need not be considered here as etiologic agents. Perhaps the most likely explanation of the infarction is the presence of previous infection in the involved lobe. There is no conclusive evidence, but the onset of pleuritic pain occurred after three weeks of respiratory symptoms. This patient's initial illness was quite likely pneumonitis which, when combined with a pulmonary embolus, resulted in an infarction.

This case demonstrates the often reiterated principle that no matter how hopeless the situation may appear clinically, every effort, including thoracotomy if necessary, should be expended to obtain a tissue diagnosis.

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EFFECTS OF SODIUM ANTIMONY TARTRATE ON THE MYOCARDIUM

Cardiograms of 59 patients receiving S. A. T. treatment were recorded before and after treatment. They showed reduction in amplitude of T, characteristic upward sloping S-T segments with terminal dipping and later frank T wave inversion, most frequently in the precordial leads V_2 to V_4 and prolongation of the Q-T duration. These changes are divided into 4 grades of severity: one patient alone showed no change, one showed grade I change, 22 grade II, 18 grade III, and 17 grade IV changes.

The changes are attributed to cumulation of antimony in the myocardium producing metabolic and functional changes and possibly actual necrosis. They are regarded as being a sign of impending clinical myocardial damage with potentially serious or lethal consequences.

It is suggested that until S. A. T. is supplanted by a safer but equally effective drug, a wise precaution is to record a cardiogram after the administration of 15-20 grains (0.9-1.2 g.) and modify the course of treatment of severe changes are seen.

Honey, M.: "Effects of Sodium Antimony Tartrate on the Myocardium," *Brit. Heart J.*, XXII:601, 1960.

THERAPEUTIC EMPLOYMENT OF PNEUMOPERITONEUM IN CERTAIN NONTUBERCULOUS DISEASES OF THE LUNGS

In clinical studies, the author shows the convincing advantage of utilizing pneumoperitoneum in suppurative diseases and traumatic affections of the lung, complicated by pulmonary hemorrhage. This treatment not only exerted a prompt hemostatic effect, but also was conducive to a clinical and anatomic recovery. A good curative effect of pneumoperitoneum was also observed in suppurative affections of the lungs coupled with tuberculosis.

Korneev, A. D.: "Therapeutic Employment of Pneumoperitoneum in Certain Nontuberculous Diseases of the Lungs," *Clinical Medicine* (USSR), XXXIX:123, 1961.

X-RAY FILM OF THE MONTH

Edited by Benjamin Felson, M.D.

The patient is a 48 year-old colored woman who came to the hospital with slight right sided chest pain, productive cough, expectoration of 300 cc. foul sputum and fever for a period of ten days. The onset was sudden. When questioned deeply, she also complained of pressure in her chest only after a heavy meal which has been promptly relieved by voluntary vomiting. Her past history was non-contributory except for a thyroidectomy in 1945.

Physical examination: poorly nourished woman of middle age; chest: moist rales and rhonchi over right upper chest posteriorly.

Sputum was negative for acid-fast bacilli on smear. *B. Proteus* colonies isolated on routine media. Skin tests 1:100 OT negative. Histoplasmin, coccidioidin, blastomycin negative.

PA chest x-ray (Fig. 1) showed a very dense shadow medially attached to the mediastinum which has a very sharp circular border laterally and inferiorly. There was infiltration and mottling of the remainder of the right upper zone with a cavitation of 3 cm. in diameter. Right lower lung field and the left side was normal. Right lateral film (Fig. 2) showed a large density in the upper chest area which was displacing the trachea considerably forward.

With these clinical and radiological findings our tentative diagnosis was mediastinal or pulmonary tumor complicated with pulmonary abscess.

Answer: ACHALASIA AND PULMONARY ABSCESS

A barium swallow solved the problem. The swallowing function was normal. The esophagus was markedly dilated. At about the second vertebral level, the esophagus took a sharp turn to the right and somewhat

FIGURE 1 FIGURE 2

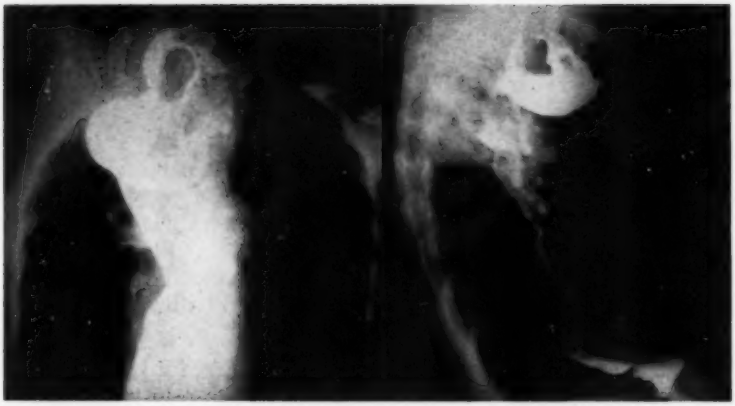

FIGURE 3 FIGURE 4

upward, then descended down towards the diaphragm. There was considerable narrowing of the cardia. No peristaltic contractions were seen. The dense shadow previously interpreted as a possible tumor was made by the enlarged esophagus (Figs. 3 and 4).

DIAGNOSIS: (1) Achalasia (mega-esophagus).
(2) Pulmonary abscess (possibly due to aspiration of esophageal contents).

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The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with brief history. Please submit material to: Benjamin Felson, M.D., chairman, Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

THE PROBLEM OF PULMONARY HYPERTENSION IN PATENT DUCTUS ARTERIOSUS

A careful correlation of clinical, radiologic, electrocardiographic and hemodynamic data will make it possible to decide to what group a patent ductus belongs; whether it be to the type with a small heart, a low pulmonary flow, great pulmonary hypertension and high vascular pulmonary resistance. This group would presumably elevate its pulmonary pressure or would show no change in it with the test of the temporary occlusion of the ductus (group I) or to the type with a large heart, a large pulmonary flow, high pulmonary pressure and low vascular pulmonary resistance. This group would show a decrease in pulmonary pressure with the test of the temporary occlusion of the ductus (group II). One might tentatively conclude that group I is the group with very high operative risk and in it the problem of hypertension does not end with the interruption of the ductus; group II is the operable group with a moderate surgical risk (10 per cent) but with excellent prognosis and virtually a total cure.

Espino Vela, J., Piccolo, E., Oliveira, E., and Rubio, V.: "The Problem of Pulmonary Hypertension in Patent Ductus Arteriosus," *Arch. Inst. Cardiol. de Mexico*, XXX:556, 1960.

SECTION ON CARDIOVASCULAR DISEASES

Straight Back Syndrome: A New Heart Disease*

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The "straight back" syndrome is a heretofore unrecognized deformity of the chest causing pseudo-heart disease. We have so named it since the condition seems to represent a congenital loss of the normal kyphotic curve of the upper dorsal spine. The flattened palm of the examiner's hand may be superimposed upon the area without deviation of the examiner's fingers. Instead of the deformity affecting the sternum as in "funnel chest," there is an incomplete inward displacement or flattening of the upper dorsal spine. This syndrome may produce pseudo-heart disease in one or two ways. First, as in funnelling of the sternum, there is decrease in the antero-posterior diameter of the chest which is most noticeable in the area of the upper dorsal spine. False heart enlargement results in the front view, particularly in the great vessel area and waist of the heart since these structures are compressed between the sternum anteriorly and the straightened, somewhat inwardly displaced dorsal spine, posteriorly (Fig. 5). Secondly, pseudo-heart disease may be produced by torsion or kinking of the great vessels. This seems to produce mechanical murmurs in systole located near the base of the heart or

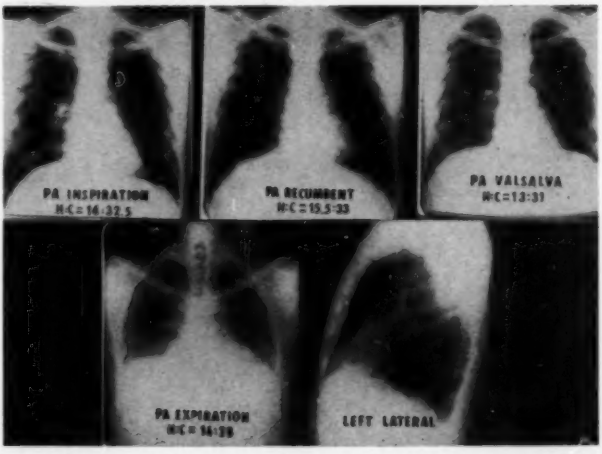

FIGURE 1: Mechanical factors causing variations in cardiac size in the same patient.

*The present manuscript is a supplement to the original article appearing in the March, 1960 issue, page 333, of the *American Journal of Cardiology*. Additional cases were collected and the present version was presented at the 26th Annual Meeting of the American College of Chest Physicians, Miami Beach, June 8-12, 1960.

**From the Diagnostic Center.

over the precordium. Both types of pseudo-heart disease appear to be completely benign in nature and congenital in origin. Rarely is the defect found without either false heart enlargement or mechanical heart murmurs.

Other Forms of Pseudo-heart Disease

The straight back syndrome is merely one type of pseudo-heart disease. Several other forms have been known for some time. False variation in heart size on x-ray film examination, for instance, may be due to mechanical phenomena. These include variations in the type of body build, the phase of heart cycle at the time x-ray film is taken, depth of inspiration, presence or absence of abdominal masses, changes in body position and many other factors.[1,2] In obese or mesomorphic individuals, the heart is frequently transverse and may at times appear enlarged. It may actually be enlarged by measurement in the transverse diameter in some cases. The vertical heart, on the other hand, may be subnormal in size, and in thin asthenic subjects, microcardia is seen occasionally.

The effects of respiration are less commonly remembered. During inspiration, the heart normally moves anteriorly toward the midline so that the retrosternal space is decreased. During expiration, the reverse occurs with the heart elevating and moving posteriorly and to the left, appearing larger. If the film is not taken during adequate inspiration, the heart tends to appear horizontal and "enlarged." These expiratory films frequently show recognizable characteristics such as closeness of the interspaces, raised diaphragms or increased bronchovascular markings (Fig. 1). Usually, six anterior ribs can be counted above the diaphragmatic level if inspiration has been adequate.

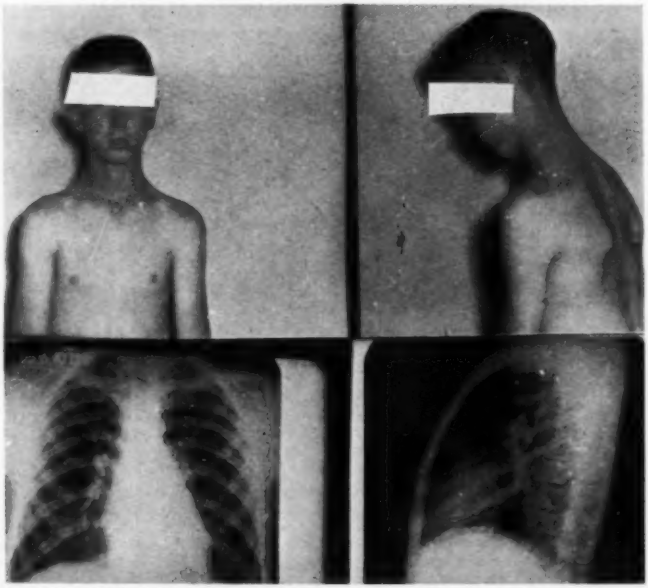

FIGURE 2: Retrosternal space decreased by the anteriorly displaced heart with secondary systolic murmur near the apex.

Heart size by x-ray film may be subject to other technical errors. For instance, if the patient is allowed to hold his breath excessively long before the picture is taken, a Valsalva maneuver may be unconsciously performed. As the breath is held, venous inflow into the heart is reduced by the increased intrathoracic pressure. Meanwhile, the heart continues to pump, pumping out the blood it contains and becoming progressively smaller with each beat. In this way, a truly enlarged heart may appear normal or actually small in size if the breath is held for a longer period than usual during routine examination of the chest (Fig. 1). Position changes also affect the heart. Since the mediastinum is quite mobile,[3] routine chest x-ray films should always be taken with the patient erect. When recumbent, the heart decreases in length, increases in width and the vascular shadows at the base of the heart widen. In pregnancy, also, there is elevation of the diaphragm and increased blood volume causing the heart to appear considerably widened.

The most frequent source of error in heart measurement, perhaps, involves the pericardial fat pad. The fat pad is of no clinical importance and is located as a triangular shadow at the apex of the heart. It should be excluded from transverse diameter measurements. Since it cannot always be identified on routine chest film, fluoroscopy is often required for proper delineation.

Other causes of pseudo-heart disease include various displacements of the heart created by congenital chest deformities or by acquired lung diseases. Not only displacements, but distortion of the heart and great vessels may be induced by chest deformities. In scoliosis of the dorsal

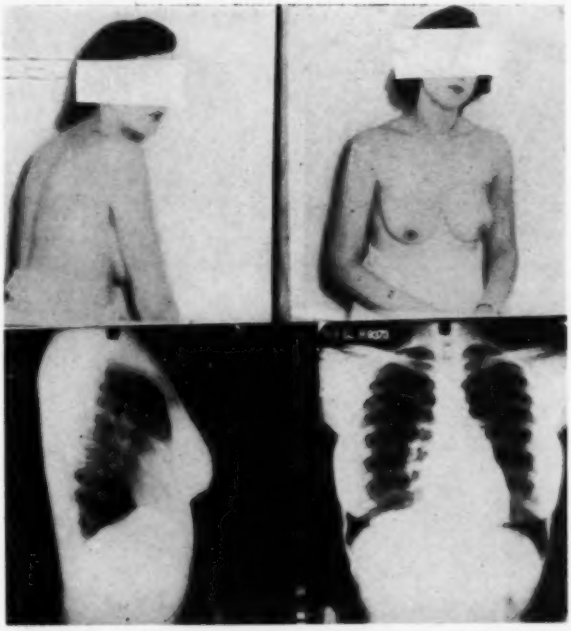

FIGURE 3: Moderate mediastinal compression causing widening of mediastinum, filling of the heart waist and a murmur resembling aortic stenosis.

spine, the heart usually is displaced opposite to the direction in which the spinal curvature is found. On the other hand, funnel chest may decrease the antero-posterior diameter of the chest, squeezing the heart between the sternum anteriorly and the spine posteriorly, displacing it somewhat to the left and pancaking its frontal view into large measurements.[3,4] Conversely, emphysema may present or obscure enlargement of the heart due to the marked vertical position and elongation of this structure. Anything causing elevation of the diaphragm, on the other hand, may cause horizontal position of the heart and apparent enlargement. These conditions include herniation, diaphragm paresis, gas, etc.

Therefore, determination of heart size and its relationships within the chest is an important part of every physical examination. Heart size cannot always be determined on routine physical examination, since a distinct point of maximal intensity of the apical beat may be absent. Percussion of the heart borders is usually inaccurate. Displacement and enlargement may be confused on physical examination. At this point, a routine chest film is usually obtained. Sometimes fluoroscopy will help when the heart and great vessels are under particular scrutiny. Dynamics are then observable and all views of the heart are possible. False heart enlargements may be reported and some true heart enlargements may be missed. The transverse diameter, for example, is the most common measurement employed in the United States and actually involves the meas-

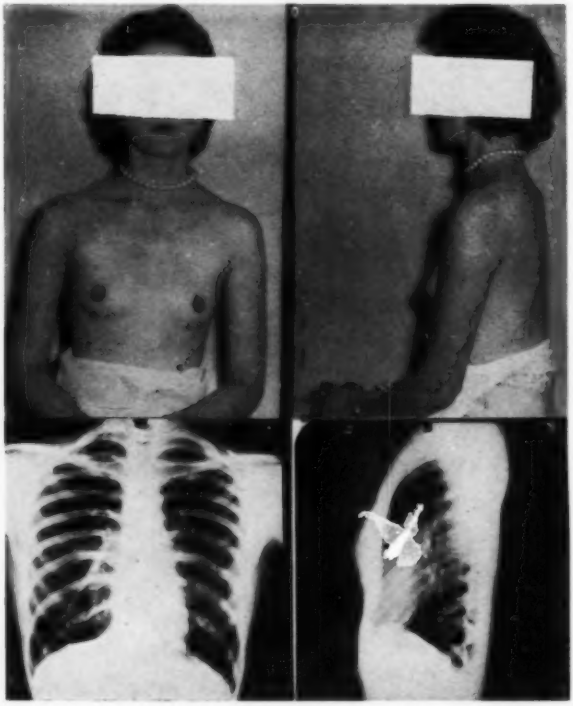

FIGURE 4: Associated murmur resembled an interventricular septal defect. The degree of straightening was not sufficient for the production of pseudocardiomegaly.

urement of three heart chambers. It is a particularly inaccurate means of measurement in borderline cases. Enlargement in this transverse diameter is frequently a late occurrence. Enlargement anteriorly or posteriorly usually occurs well before transverse widening becomes evident Lateral x-ray views may show this. Conversely, false enlargement of the heart may be confused with true heart enlargement in the frontal view unless lateral x-ray films are taken in these cases.

Clinical Cases of the Straight Back Syndrome

During a period of four years in a moderate-size city, we have gathered 12 cases of straight back syndrome which had been masquerading as heart disease. It has yet to be determined what the incidence would be in the general population.

The degree of deformity found in this syndrome varied from mild cases with torsion murmur and no enlargement to severe cases with actual widening of the heart shadow. The less severe cases (Fig. 2) were more frequent and usually presented slight, harsh, late systolic murmurs over the base of the heart. There was also an increased pulmonic closure sound in most cases and x-ray films usually showed a "filling" of the waist of the heart. This filling fluoroscopically represented rotation

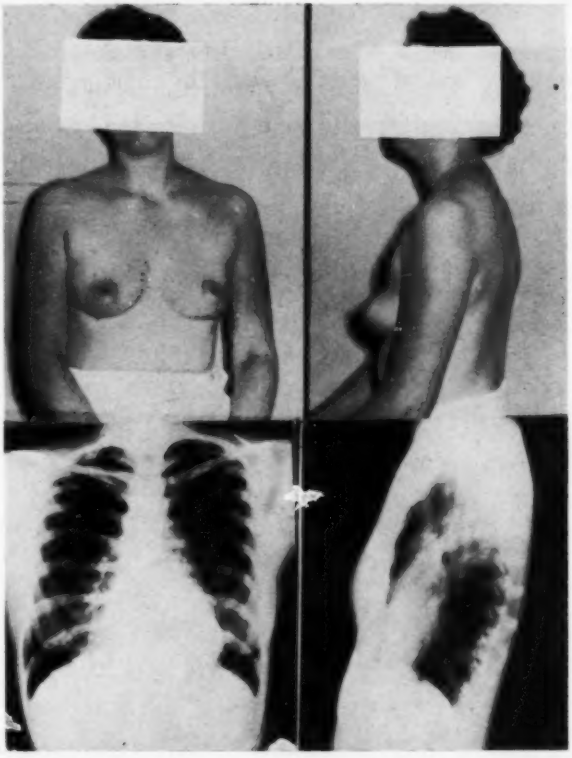

FIGURE 5: Straight back syndrome with associated marked mediastinal compression and pseudocardiomegaly.

and impingement of the pulmonary conus against the retrosternum in the area of the murmurs. The dorsal spine was straightened and seemed to be a constant clinical finding in these cases. Actual physical grooving or funnelling of the spine rarely occurred.

One of the patients (Fig. 3) had been refused life insurance because of a harsh systolic murmur persisting at the base of the heart. At first, rheumatic fever had been suspected and as a result, she spent six weeks at bedrest. The mechanical defect of straight back syndrome was evident and the usual pathologic causes for the murmur were excluded by catheterization and other appropriate tests. A diagnosis was made of benign murmur of no consequence. The insurance company then awarded the policy free of riders and restrictions.

An interventricular septal defect had been diagnosed previously in another patient (Fig. 4). She had been living with a delusion of serious heart disease all of her adult life. Pregnancy had been purposely avoided, recreational activities limited, and she had been leading a rather secluded life. Clinical studies and cardiac catheterization showed no abnormality.

One of our larger manufacturing plants had refused employment to one patient (Fig. 5) because of heart enlargement. Routine examination showed a straightened dorsal spine. When the lateral film of the chest was taken, it became evident that heart compression was causing false heart enlargement in the frontal view. The patient was given cardiovascular clearance and was then accepted for employment.

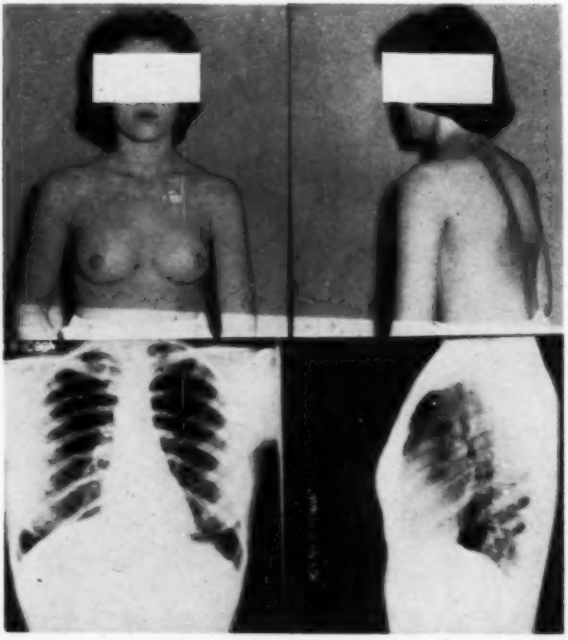

FIGURE 6: Systolic precordial murmurs in young female with characteristic large breasts, flaring ribs and absent retrosternal space found in this syndrome.

Another pre-employment physical examination resulted in disqualification of an otherwise healthy 18-year-old woman because of a precordial systolic murmur. When the straight back syndrome was noticed on physical examination, a lateral chest film was taken, revealing an obliterated retrosternal space. There was no other abnormality found in accessory examinations (Fig. 6).

Discussion

Differentiation of true and false heart enlargement in routine chest x-ray films is best made by obtaining a lateral view of the chest to demonstrate heart compression or "pancaking" induced by the narrowed antero-posterior diameter of the chest. Normally, the degree of impingement upon the retrosternal space varies with the shape of the thorax, the degree of inspiration (when it is closer to the sternum) and the amount of pericardial fat or obesity. To be included in this list now will be the "Straight Back syndrome" in which the retrosternal space is usually obliterated.

Often the degree of straight back deformity is insufficient to produce heart shadow enlargement, but is sufficient to compress the aortic arch or impinge upon the main pulmonary trunk to create mechanical murmurs. The pulmonary conus lies against the inner surface of the sternum in most of these cases, and perhaps could transmit sounds more readily for this reason. The aorta, anchored at the root of the heart and at the diaphragm, is subject to torsions at the level of its arch and could conceivably create murmurs.[2,7] Moreover, the straight back syndrome tends to feature an aorta that descends completely anterior to the dorsal spine, appearing to be a more midline structure than usual. The exact etiologic mechanism of the murmur found in this syndrome, however, is not clear.

Perhaps the defect might begin in the eighth week of fetal life before ossification occurs in the bodies of the vertebrae. Perhaps the failure of development of the normal dorsal kyphosis could be a common occurrence when compared with the multiplicity of many other spinal defects that frequently appear.[8] Perhaps the completely straightened spine that characterizes the normal infant fails to develop the expected postural curves of adulthood for other reasons. It is conceivable that the degree of deformity could also be limited by the thoracic cage itself due to the splinting effect of the ribs

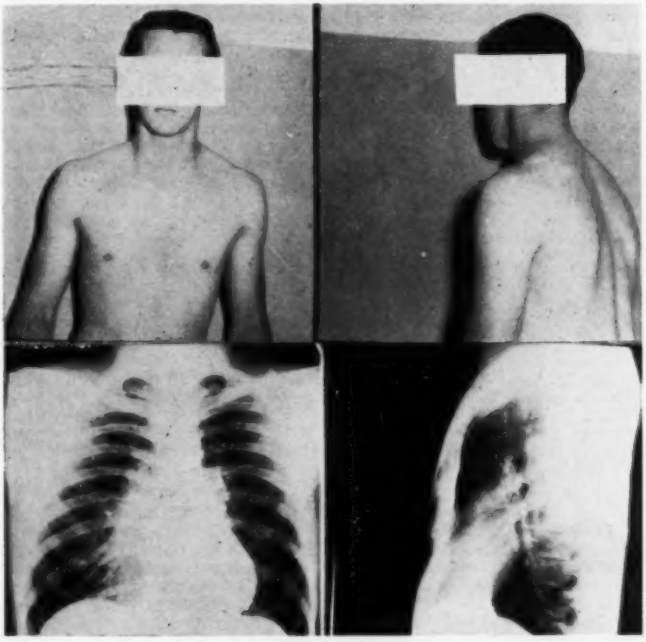

FIGURE 7: The association of straight back syndrome and funnel chest syndrome in the same patient, suggesting developmental origins of both.

upon movements in the dorsal spine. Nevertheless, helping to confirm the developmental origin of the straight back syndrome, is one case we found in which there was an associated mild funnel chest deformity (Fig. 7).

Many other factors could also have influence upon the development of the apparent enlargement of the heart. Perhaps there is an associated persistence of the globular heart of the infant into the adult silhouette. Perhaps also, the depth of the chest fails to increase as the body in general continues to grow. Another possibility is the resemblance of the heart silhouette found in recumbency to that found in the straight back syndrome. During recumbency, the cardiac silhouette widens considerably as gravitation effects cause the heart and great vessels to rest toward the dorsal spine posteriorly.[9] Perhaps this is why most functional murmurs seem to increase during recumbency. This is still a matter of conjecture, and needs a means of objective evaluation.

Although it is known that cardiorespiratory failure may result from various chest deformities causing distortion of the heart or kinking of the great vessels, we have not observed any tendency to decompensation with this new syndrome. Perhaps this can be likened to the rarity of heart failure in pectus excavatum[10] compared to its relative frequency in kyphoscoliosis.[11]

SUMMARY

A new syndrome of heart disease has been presented that we have not found recorded in the literature heretofore. We prefer to call this the "straight back" syndrome. It may be described as a congenital straightening of the upper dorsal spine which decreases the anteroposterior diameter of the chest at this level. This results in compression phenomena which may either cause pseudocardiomegaly or cause mechanical murmurs. These murmurs are systolic in timing and would seem secondary to distortion or impingement of the great vessels. Simple physical examination will usually reveal the straight back syndrome. The degree of deformity may then be determined when lateral x-ray films are taken. The simple defects found in this syndrome may not be uncommon. Their recognition may prevent a common form of iatrogenic heart disease that has often interfered with employment, insurability and peace of mind.

RESUMEN

Se ha presentado un nuevo síndrome de padecimiento cardiaco que no se hallaba antes en la literatura. Preferimos llamarlo el síndrome de la "Rigidez Dorsal" (Straight Back). Puede describirse como una rigidez congenita de la espina dorsal en su parte superior que hace disminuir el diametro anteroposterior del torax a esa altura. Esto trae como consecuencia fenómenos de compresión que pueden causar ya sea pseudocardiomegalia o murmullos mecánicos.

Estos murmullos o soplos son sistólicos y parecen secundarios a distorsión o compresiones de los grandes vasos. El exámen físico simple revelará generalmente este síndrome. El grado de deformidad puede ser determinado cuando se hacen radiografías laterales. Los defectos simples encontrados en este síndrome pueden no ser raros. Su reconocimiento puede evitar una forma común de enfermedad iatrogénica que a menudo ha sido motivo de interferencia para el empleo, para el aseguramiento o para la tranquilidad.

RESUMÉ

L'auteur présente un nouveau syndrome d'affection cardiaque qui ne semble pas avoir été jusqu'à présent rapporté dans la littérature. Il peut être décrit comme un rétrécissement congénital de l'épine dorsale supérieure, qui diminue le diamètre antéropostérieur du thorax à ce niveau. Il en résulte des phénomènes de compression qui peuvent soit être cause d'une pseudocardiomégalie soit de souffles mécaniques. Ces souffles sont systoliques en chronométrant, et sembleraient secondaires à une distorsion ou un choc des grands vaisseaux. Un simple examen physique révélera habituellement ce syndrome. Le degré de déformation peut être déterminé après des clichés radiologiques de profil. Les simples altérations trouvées dans ce syndrome sont peut-être assez fréquentes. Leur connaissance peut éviter de croire à une forme commune d'affection cardiaque qui entraine souvent des conséquences professionelles, ou portant sur la sécurité et la tranquillité d'esprit.

ZUSAMMENFASSUNG

Es wurde über ein neues Syndrom einer Herzenkrankung berichtet, von dem wir bisher noch keine Mitteilung in der Literatur gefunden haben. Wir schlagen vor, es "Rückenstreck-" Syndrom zu benennen. Es läßt sich beschreiben als ein angeborenes Strecken der oberen Brustwirbelsäule, das zu einer Verengerung des anterioposterioren Durchmessers des Brustkorbes in dieser Höhe führt. Dieses hat Kompressions-Phänomene zur Folge, die entweder eine Pseudocardiomegalie oder mechanische Herzgeräusche verursachen können. Diese systolischen Geräusche können die Folge einer Distorsion oder eines Druckes auf die großen Gefäße sein. Die enifache physikalische Untersuchung wird für gewöhnlich das Rückenstreck-Syndrom aufdecken. Das Aus-

maß der Deformität läßt sich dann ermitteln, wenn Thorax-Röntgen-Queraufnahmen gemacht werden. Die einfachen, bei diesem Syndrom auftretenden Defekte sind vielleichnicht ungewöhnlich. Ihre Feststellung kann eine häufige Form einer iatrogenen Herzkrankheit verhindern, die oft in Konflikt gerät mit der beruflichen fätigkeit, der Krankenversicherung und dem Seelenfrieden.

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PULMONARY ARTERIOVENOUS FISTULA AND CARDIAC HYPERTROPHY

1. A report is made on the post-mortem findings in a patient with pulmonary arteriovenous fistulas who died of congestive cardiac failure 11 years after multiple pulmonary resections.

2. Generalized cardiac hypertrophy, without further cardiac lesions, was encountered. The enlargement was apparently the result of increased output.

3. Cardiac hypertrophy is an uncommon consequence of pulmonary arteriovenous fistulas but may be present in cases with large fistulas.

4. Large shunts may be responsible for the increased cardiac output; however, data on output in conjunction with this disease are contradictory and the mechanisms giving rise to such an increase have not yet been duly elucidated.

Ruedy, J. R., and Israel, H. L.: "Pulmonary Arteriovenous Fistula and Cardiac Hypertrophy," *El Torax*, IX:119, 1960.

PATHOLOGIC CHANGES IN THE LIVER RESULTING FROM PRESSURE EXERTED BY PLEURAL EFFUSION ON THE RIGHT SIDE

Hepatic functional changes were studied which resulted from accumulation of a large pleural effusion on the right side. Pertinent examinations consisted of laboratory tests, such as serum colloids, proteinemia, hematocrit, clinical and radiologic findings and transthoracic liver biopsy.

As a control, cases of left pleural effusion have been examined. It was observed that the positivity of clinical and laboratory data corresponds to the type and entity of the histologic lesion and that the liver changes undergo a marked improvement after elimination of the right pleural effusion. Such data lead to the conclusion that the liver is affected not only by the disease in question, but also by the mechanical pressure of the right effusion and that its damage is to be evaluated on the basis of liver semeiology and laboratory analysis.

Zampori, O.: "Pathologic Changes in the Liver Resulting from Pressure Exerted by Pleural Effusion on the Right Side," *Riv. Pat. Clin. Tuberc.*, XXXIII:730, 1960.

The Present Status of Open Heart Surgery by Means of the Pump Oxygenator*

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Six years have passed since Gibbon made the first successful application of extracorporeal circulation for the repair of an atrial septal defect in a human patient. Since that time, a wide field of cardiac surgery has been opened. Now, most congenital heart diseases are not only surgically treatable, but are able to be cured with relative safety.

In an attempt to determine the present status of extracorporeal circulation in the world, including its popularity, indications, safety, and limitations in open heart surgery, a survey was undertaken. The purpose of this paper is to report an analysis of the data collected from the survey. The questionnaire was sent to 54 noted cardiac surgeons in the world. A reply was received from 37 (68.5 per cent of the total). The analysis of the present status of the pump oxygenator in open heart surgery is based on this survey.

Open heart surgery using the pump oxygenator has been widely accepted and there are many surgeons who already have considerable experience with this type of surgery in the United States. However, it is still limited mainly to university hospitals in other countries (Table 1).

Types of Pump Oxygenator

There are three types of pump oxygenators—bubble, film and membrane. There are two different kinds of the film type—one is the screen type introduced by Gibbon, the other a disc type by Kay-Cross. The bubble type oxygenator, devised by DeWall-Lillehei, promoted a spread of extracorporeal circulation because of its simplicity and efficiency, and various modifications of it have been made by many. However, it is apparent that this type of pump oxygenator is being replaced gradually by other types. Gross[1] states there is little doubt that the bubble oxygenator will gradually fall into discard. This survey also clearly showed that trend. The disc and screen types are the two most commonly used at present. In Japan, the bubble type is almost exclusively used, probably because of economic reasons. The membrane type of Clowes is ideal in principle, but is only used by a few at present.

Flow Rate in Total Body Perfusion

In the early stage of development of the pump oxygenator, low flow rate was preferred by Lillehei. However, many studies showed that high flow is better than low flow to keep the patient in a more physiologic condition during extracorporeal circulation. Metabolic acidosis, which was considered one of the major causes of death due to total body perfusion, can be eliminated with high flow which is almost close to normal

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cardiac output. The survey clearly showed that the current trend is to use high flow. Many prefer a low rate of 100 cc./kg./min. or 2.3L./M²/min. or more. However, it is apparent that a few, such as Lillehei and Cooley, are still using the low flow rate with excellent results.

Time of Circulatory Cessation

Although in the early stages of the pump oxygenator, circulatory cessation was limited to a period only slightly longer than hypothermia,

TABLE 1—PRESENT STATUS OF OPEN HEART SURGERY BY PUMP OXYGENATOR

Surgeon	Type of Oxygenator	Flow Rate (cc./kg./min)	Elec. Cardiac Arrest	Hypothermia	Cases
Lillehei	bubble	50-100	—	—	900
Cooley	bubble	50	—	—	725
Kirklin	screen	high	potassium	—	440*
Lam	bubble	75-100	acetylchol.	—	319
Effler	disc	100	potassium	—	300
Sirak	disc	80-130	potassium	—	232
Kay, E. B.	disc	medium	potassium	—	200*
Maloney	screen & disc	70-110	—	—	200
Gross	disc	2.3 L/m²	—	—	200
Duke Univ.	bubble	25-50	potas. mag, prostig.	+	156
Hanlon	disc	100	occasionally	—	145
Kent	disc	high	selective	—	137
Potts	disc	2 L/m²	potassium	—	127
Kay, J. H.	screen	high	—	—	123
Sloan	disc	2.3 L/m²	—	—	122*
Dodrill	screen	70-75	—	—	105
Harken	disc	high	acetylchol.	+	100
Gerbode	screen & disc	100	—	—	100
Merendino	bubble	2.2 L/m²	—	—	100
Nelson	disc	2.3 L/m²	potassium	—	65
Clowes	membrane	75	seldom	+	51
Sanger	disc	70-90	acetylchol.	—	51
Bahnson	screen	2.3-3 L/m²	—	—	50
Scannell	disc	70-100	potassium	—	44
Creech	disc	high	—	—	
Kirby	screen	110	—	—	
Bigelow	bubble	80	—	+	55
Dubost	bubble	80-100	potassium	—	170
Crafoord	Crafoord-Senning	75-140	—	+	140
Zenker	screen	2-2.4 L/m²	potassium	—	68
Linder	screen	2.3 L/m²	—	—	42
Derra	screen	1.9-2.5 L/m²	—	+	32
Brock	bubble	high	—	+	
Sakakibara	bubble	20-40	potassium	+	219
Manabe	bubble	60-100	—	—	64
Kimoto	bubble	50-170	—	—	43
Inoue	bubble	37-70	—	—	few
Sugie	bubble	80-100	—	—	few
Wada	bubble	40-60	—	—	few
Huke	disc	50	—	—	few
Sunada	bubble	60-90	—	—	few

Based on data supplied personally by recent survey (Aug. 1959) except *
*References, 7, 16, 17 in order

it is presently able to be used as long as 30 minutes. Many have reported survival where circulatory cessation was sustained for more than one hour.

Physiologic Changes in Total Body Perfusion

There are many problems relating to physiologic changes during or after total cardiopulmonary bypass. Changes in acid-base balance, blood volume, body temperature and blood chemistry were important and debatable points in the early stages of extracorporeal circulation. Some of them are now less serious problems with increased experience. It was made clear by Clowes and others that metabolic acidosis, which related to body perfusion, was due to tissue anoxia from insufficient flow.[2] Fall of body temperature, which inevitably accompanied perfusion, is minimized by warming the circulating blood, although some are not concerned about it and intentionally depress the temperature to a lower level.[3,4] Postoperative bleeding is not a serious problem for the experienced surgeon now. It is important to keep changes in blood volume at a minimum during the pre- and postperfusion period. Some recommend measurement of body weight pre- and postoperatively, although others do not recognize its significance.[5,6] However, blood volume usually should be kept constant by accurately replacing any blood loss during perfusion.

Monitoring During Perfusion

There is no reliable method to evaluate the condition of the patient during perfusion, although many devices are used. Electrocardiogram, electroencephalogram, measurement of arterial, venous pressure and arterial blood pH are currently used as monitors during perfusion. Many are satisfied to keep the blood pressure above 80 mm.Hg. and venous pressure below 15 mm.H_2O. However, these can be omitted with added experience, as Gross suggests.[1]

Indication for and Results of Extracorporeal Circulation in Open Heart Surgery

Some feel that almost all types of congenital heart disease should be corrected under direct vision by means of the pump oxygenator. On the

TABLE 2—RESULTS IN ATRIAL SEPTAL DEFECT (OST. SECUND.)

Surgeon	Op. Method	No. of Cases	Death	
			No.	per cent
Cooley	Pump-Oxygenator	152	8	5
Lillehei	Pump-Oxygenator	104	1	0.9
Sakakibara	Pump-Oxygenator and Hypothermia	72	5	7
Sirak	Pump-Oxygenator	45	2	4.4
Dubost	Pump-Oxygenator	36	2	5.6
Hanlon	Pump-Oxygenator	35	2	5.7
Derra	Hypothermia	130	9	6.9
Swan	Hypothermia	100	7	7
Lewis	Hypothermia	62	6	9.5
Bedford	Hypothermia	50	1	2
Kirklin	Atrial Well	140	3	2.2
Kimoto	Brain Cooling	36	1	2.7

other hand, some prefer simpler methods such as hypothermia for repair of secundum type of atrial septal defect or isolated valvular pulmonary stenosis.

An operative mortality of 40 to 60 per cent was not rare in the early stage of the pump oxygenator in 1955-56. Marked improvement, however, was attained with increased experience, justifying its wide application to most of the common types of congenital heart diseases.

Atrial Septal Defect

There is no doubt that uncomplicated atrial septal defects can be managed safely under direct vision with hypothermia. Kirklin[7] is still a patron of the atrial-well method of Gross for uncomplicated atrial septal defect, although Gross has already discarded his own device and recommends extracorporeal circulation. Lillehei[8] advocates the use of the pump oxygenator for all types of atrial septal defects as well.

It is remarkable that no significant difference in results was found between these methods when each person used the method to which he was accustomed. However, operative mortality is still high in the primum type of atrial septal defect or so-called A-V canal, which is a clear indication for the use of the pump oxygenator, even when the operation is performed by an experienced surgeon.

Ventricular Septal Defect

Ventricular septal defect is a clear indication for the use of the pump oxygenator and the results are also good, with an average mortality of 15 per cent. However, mortality is very high in cases accompanied by significant pulmonary hypertension exceeding 75 per cent of systemic blood pressure (Table 4). Some methods, as gradual closure of septal defects with a perforated Ivalon patch, have been attempted recently in managing these patients, although none of them is considered to be secure.[9]

TABLE 3—RESULTS IN VENTRICULAR SEPTAL DEFECT (Pump-Oxygenator)

Surgeon	No. of Cases	Death No.	Death per cent
Lillehei	154 (1954-56)	45	29
	67 (1957)	10	15
	105 (1958)	5	4.7
Kirklin	186		
	20 (1955)	4	20
	70 (1957)	8	12
Cooley	236	32	13
Lam	150	31*	21
Potts	75	5**	7
Sirak	75	5**	7
Sakakibara	74	13	18
Kay, J. H.	51	4	8
Dubost	34	8	24

*10 per cent over two years of age
**All associated with pulmonary hypertension

TABLE 4—RESULTS IN PULMONARY VALVULAR STENOSIS

Surgeon	Op. Method	No. of Cases	Death	
			No.	per cent
Sirak	Pump-Oxygenator	42	0	
Lillehei	Pump-Oxygenator	37	1	3
Cooley	Pump-Oxygenator	32	3	9
Kirklin	Pump-Oxygenator	31		
Hanlon	Pump-Oxygenator	30	1	3
Derra	Hypothermia	54	3	5
Swan	Hypothermia	38	2	5
Lam	Direct Vision Normothermia	50	1	2

Elective cardiac arrest by the Melrose technique, which was widely employed during the repair of ventricular septal defect at one time, has now been discarded and anoxic arrest is preferred by many at the present time.

Pulmonary Stenosis

Isolated valvular pulmonary stenosis is easily corrected within a few minutes of circulatory cessation by hypothermia. Recently, Lam[10] reported direct vision repair of this anomaly under normothermia with excellent results. Some still prefer the closed method of Brock. On the other hand, Kirklin[11] recommends the pump oxygenator, insisting that valvular pulmonary stenosis is often associated with infundibular stenosis; hence, complete relief of stenosis can be achieved with added infundibulectomy.

There is no marked difference in the early results between various methods, although follow-up results are not yet clear (Table 5). There is no doubt that isolated infundibular stenosis should be corrected with the pump oxygenator, although it can be done under hypothermia.

Tetralogy of Fallot

The present development of cardiac surgery was promoted by an ingenious operation for Tetralogy of Fallot by Blalock and Taussig.

TABLE 5—RESULTS IN TETRALOGY OF FALLOT (Pump-Oxygenator)

Surgeon	No. of Cases	Death	
		No.	per cent
Lillehei	25 (1954-55)	10	40
	72 (1956-57)	13	18
	38 (1958)	3	8
Kirklin	74	21	28
	5 (1954-55)	5	100
	69 (1956-)	16	23
Cooley	58	14	24
Kay, J. H.	35	7	20
Potts	32	10	31
Riker	30	5	17
Hanlon	25	11	44
Dubost	21	7	33

The shunt operation is now considered classic and is the secondary choice of surgical treatment for Tetralogy of Fallot. Lillehei[9] and Kirklin[10] insist that the shunt operation should not be done except in special cases and that Tetralogy of Fallot should be corrected under direct vision by the pump oxygenator. Accumulated data show that the results of radical surgery are better than those of the shunt operation. However, operative mortality is still so high, even in experienced hands, such as Lillehei or Kirklin, that general application of the radical method is considered to be premature.

Acquired Heart Disease

Recently many have tried to correct acquired valvular disease, especially mitral insufficiency, aortic stenosis and insufficiency, under direct vision with the pump oxygenator, although the results are not as good as in congenital heart disease (Table 6).

Combination of Pump Oxygenator with Hypothermia

A combination of hypothermia with the pump oxygenator is still a controversial problem. Many prefer maintaining normothermic condition during extracorporeal circulation, although some feel that the combination may be valuable in special cases: for example, in severe Tetralogy of Fallot. However, there are some people who routinely use hypothermia combined with the pump oxygenator (Table 1). They use relatively low flow for perfusion with excellent results. Also, heat exchangers are used for rapid cooling and rewarming by some.

Complications of Extracorporeal Circulation

It is not always easy to analyze the causes of death by extracorporeal circulation due to complex nature of the procedure. Metabolic acidosis, postoperative bleeding, complete heart block, respiratory complications, cardiac failure and the so-called postperfusion syndrome are considered to be complications which are frequently encountered in open heart surgery while using the oxygenator. Complete heart block, which is frequently associated with repair of ventricular septal defect, may be avoided by improving operative technique. Some advocate the use of the pace-

TABLE 6—RESULTS IN ACQUIRED HEART DISEASE (Pump-Oxygenator)

Surgeon	Lesion	No. of Cases	Survival	Death
Crafoord	AS	13	10	3
	MI	10	3	7
Scannell	AS	17	9	8
	MS	5	3	2
	MI	2	2	0
Riker	AS	21	15	6
Harken	MI	18	13	5
	Combined	15	9	6
Clowes	MI	10	8	2
	AS	5	4	1
Bigelow	MI	10	6	4

MS: Mitral Stenosis AS: Aortic Stenosis MI: Mitral Insufficiency

maker under such circumstances, while others recognize no appreciable advantages in it. Postperfusion syndrome, where gradual deterioration of the patient's condition occurs postoperatively, despite successful operation, is considered to be caused by microscopic embolism of brain tissue. Its incidence varies with various types of oxygenator and decreases with experience. Although Lillehei recently stated that he has never seen such a complication, further study is required.

SUMMARY

A survey of the present status of extracorporeal circulation in open heart surgery revealed that the pump oxygenator has been widely accepted around the world, and various kinds of heart disease, especially congenital, have been cured surgically with a reasonable degree of safety. The film-type oxygenator, either disc or screen, is the one most commonly used. High flow rate, nearly equivalent to cardiac output in the normal circulation, is considered advantageous in total body perfusion. The combination of hypothermia with the pump oxygenator is still a debatable issue.

RESUMEN

El estudio del estado actual de la circulación extracorpórea en la cirugía en corazón abierto reveló que el oxigenador de bomba ha sido aceptado ampliamente en todo el mundo y varias clases de enfermedades del corazón especialmente congénitas se han curado quirúrgicamente con un grado razonable de seguridad. El oxigenador de lámina ya sea por el uso de discos o de pantallas es uno de los mas comúnmente usados. Se considera ventajosa al paso de la corriente sanguínea a una velocidad equivalente al rendimiento cardiaco en la circulación normal cuando se hace perfusión corporal completa. La combinación de hipotermia con el oxigenador de bomba es aún discutible.

RESUMÉ

Une enquête sur l'état actuel de la circulation extracorporelle dans la chirurgie à coeur ouvert a révélé que l'oxygénateur à pompe est largement accepté à travers le monde et que différentes sortes d'affections cardiaques, particulièrement congénitales, ont été guéries chirurgicalement avec une proportion de risque raisonable. L'oxygénateur "film-type" soit à disque, soit à écran, est un des plus communément utilisé. Un taux élevé de débit circulatoire, presque équivalent au débit cardiaque dans la circulation normale, est considéré comme avantageux dans la perfusion totale. L'association de l'hypothermie avec l'oxygénateur à pompe est un procédé qui est encore objet de discussion.

ZUSAMMENFASSUNG

Eine Übersicht über den gegenwärtigen Stand des extrakorporalen Kreislaufes bei Operationen am offenen Herzen führte zu dem Schluß, daß der Pumpen-Oxygenator auf der ganzen Welt in großem Umfang Eingang gefunden hat. Es wurden verschiedene Arten von Herzkrankheiten, besonders in angeborener Form, auf chirurgischem Wege geheilt mit einem angemessenen Grad von Sicherheit. Der Oxygenator-Typ mit Film, entweder als Platte oder Gitter, wird am häufigsten benutzt. Die hohe Durchströmungsgeschwindigkeit, welche nahezu mit dem Herzminutenvolumen in der normalen Zirkulation adäquat ist, wird für die Durchblutung des gesamten Körpers als ein Vorteil angesehen. Die Kombination der Unterkühlung mit dem Pumpenoxygenator bleibt noch ein anfechtbarer Sachverhalt.

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ANTHROPOLOGIC FACTORS AFFECTING THE ESTIMATION OF EXPOSURES REQUIRED FOR CHEST RADIOGRAPHS

Some form of automatic exposure control is necessary to produce correctly exposed films. In the absence of such control, the use of a nomogram based on the antero-posterior diameter, weight and stem height, will give a useful approximation of the correct exposure.

Some patients produce photographically substandard films consistently; it is possible these films may reflect their physiologic state rather than errors in exposure.

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Pulmonary Hypertension of Unknown Cause*

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Pulmonary hypertension occurs in a variety of conditions. It may exist as a congenital anomaly with or without an associated cardiac defect, or it may be acquired. One classification of acquired pulmonary hypertension is that suggested by Wood,[1] including: (1) passive, (2) hyperkinetic, (3) obstructive, (4) obliterative, (5) vascoconstrictive, and (6) polygenic.

Congenital pulmonary hypertension is usually found in association with intracardiac defects and persists from birth. Some cases of isolated or unexplained pulmonary hypertension have been described in very young children with cardiac symptoms from birth and must be accepted as a congenital "primary" pulmonary hypertension.

Hypertrophy of the right ventricle in the absence of any obvious cause was first described by Romberg[2] in 1891. From that time until the beginning of the era of heart catheterization in 1941,[3] there was much dispute as to the relationship of hypertension of the lesser circulation to hypertrophy of the right ventricle. Many of these cases were published under such titles as "Right Ventricular Hypertrophy of Unknown Origin,"[4] "Primary Pulmonary Vascular Sclerosis,"[5,6] and "Isolated Hypertrophy of the Right Ventricle of the Heart of Unknown Cause."[7]

Since 1941, there have been many cases studied by right heart catheterization and proved at post-mortem examination. In 1951, Dresdale *et al.*[8] were able to find ten reported cases of pulmonary hypertension without discernable cause that had been studied by right heart catheterization. Since their report there have been many cases of unexplained or primary pulmonary hypertension in tabulations of cases encountered in catheterization laboratories.[9,10] Several reviews have been published.[11-13]

Recently we have had the privilege of studying a patient who developed unexplained pulmonary hypertension while being followed at the University of Minnesota Hospitals for an unrelated condition. This made it possible to obtain an interesting series of electrocardiograms (Fig. 1) and chest x-ray films (Figs. 2, 3, 4, and 5) that demonstrate the evolution of the disease. The patient was studied by right heart catheterization and material was obtained for pathologic study by open lung biopsy.

Case Report: Mrs. M. P., a 42 year-old white woman, had been followed since 1948. At that time, she was found to have anemia, neutropenia, and bone marrow that showed a maturation arrest of the granulocytic series with a normoblastic hyperplasia. A history of benzol exposure in 1945 was obtained, and she was thought to have bone marrow depression secondary to benzol exposure. No cardiac abnormality was noted on physical examination and chest x-ray film and ECG were normal.

She was found to have splenomegaly in 1952 and splenectomy was done. Again, no cardiac abnormality was noted and the chest x-ray film (Fig. 2) and ECG were normal. She was followed in the hematology clinic for the next three years with no specific complaint except for tiredness and a vague ache between her shoulder blades. Her hemoglobin was in the range of 11.0 to 12.5 Gm. during this time.

In May, 1955, she began to complain of a vague, aching, substernal pain that was usually associated with exercise and relieved by rest. This pain was not relieved by

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nitroglycerin and lasted longer than 10 to 15 minutes. The ECG (Fig. 1) was still normal, although the T wave had become inverted in V-1 through V-3. A Grade I apical systolic murmur was described.

In March, 1957, she developed a dry, chronic cough with occasional hemoptysis. Chest x-ray films (Fig. 4) were consistently normal and she was thought to have chronic bronchitis. In October, 1957, she complained of palpitation, dyspnea, and weakness on effort. An ECG at that time (Fig. 1) showed moderate T wave inversion in III, aVF, and V-1 through V-3 with ST depression in V-2 and V-3. A subendocardial infarction was suspected, but follow-up ECG's were unchanged and none of the other signs of myocardial infarction was found.

She noted gradual increase in weakness, palpitation, exertional dyspnea and chest pain during the next year. She was again seen in February, 1958, with the same complaints, was found to have no cardiac enlargement, clear lungs, and a soft Grade I apical systolic murmur. Her symptoms continued to increase until the later part of 1958, when she developed orthopnea, ankle edema, cyanosis and increased chest pain on effort. She was admitted to the hospital in October, 1958, for further diagnostic studies.

She was described as a thin, nervous, white woman in mild respiratory distress. There was slight cyanosis of the lips and nail beds at rest that became much more prominent on exercise. The vital signs were normal. There were a few petechiae over the skin of the chest. The lungs were clear to percussion and to auscultation. The heart was slightly enlarged to the left and there was a prominent right ventricular impulse just to the left of the sternum. The pulmonic second sound was palpable. There was a normal sinus rhythm with a blowing, Grade III systolic murmur heard over the entire precordium, but heard best just to the left of the sternum in the third and fourth intercostal spaces. The pulmonic second sound was much louder than the aortic and was widely split and fixed. There was no diastolic murmur either down the left sternal

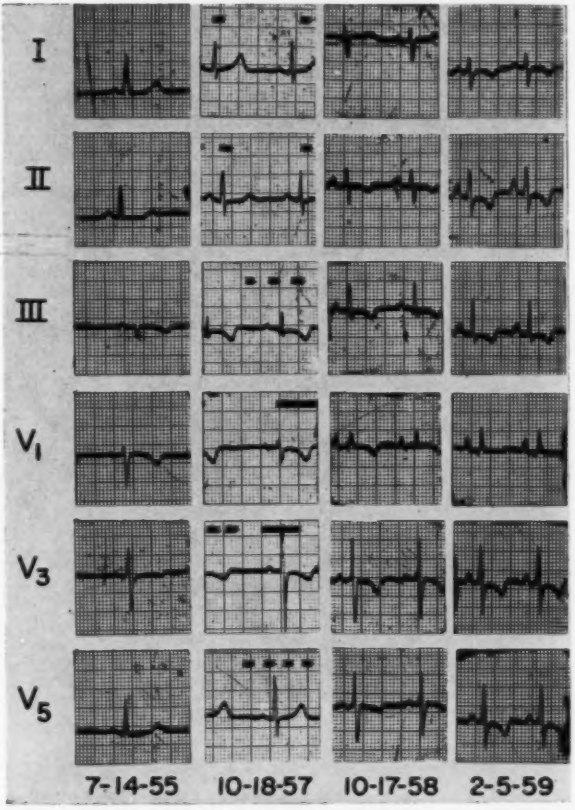

FIGURE 1: Serial ECGs from July, 1955 through February, 1959 showing the evolution of the right ventricular hypertrophy and strain pattern.

TABLE 1

Pulmonary Function Tests		
Tidal Volume	— 500-575 ml.	
Rate	— 15	
Minute Volume	— 8 l/min.	
	Observed	Per cent of Predicted
Inspiratory Capacity	1500	88
Expir. Res. Volume	850	
Vital Capacity	2500	108
Residual Volume	600	
Total Lung Capacity	2900	
Timed Vital Capacity		
1st second	1800	75 per cent
2nd second	2070	87 per cent
3rd second	2200	93 per cent
Total	2400	
Maximum Breathing Capacity 60 L./min. 100 per cent of predicted		
CONCL: Essentially normal respiratory function.		

border or at the apex. The liver was palpable 4 cm. below the right costal border and there was one plus pitting edema of the ankles.

The hemoglobin was 15.7 gm. and the white blood count was 8950 with 25 neutrophiles, 67 lymphocytes, 4 monocytes, 3 eosinophils and 1 basophil. The urinalysis was negative and the blood urea nitrogen, fasting blood sugar, total serum proteins and albumin/globulin ratio were normal. The blood Kline reaction was negative. The platelet count was 180,000 per cu. mm. and the clot retraction was normal. The red cells were mildly macrocytic and hyperchromic and the reticulocyte count was 5.6 per cent. Free acid was found on gastric analysis, and the bone marrow examination was unchanged. All of the liver functions tests were normal as were bleeding, clotting and prothrombin times. Prior to exercise, the arterial oxygen saturation was 91.2 per cent. This fell to 78.6 per cent after mild exercise. The venous pressure was 130 mm. of saline solution and the arm to tongue circulation time was 27 sec.

Cardiac fluoroscopy (Fig. 5) was thought to show biventricular enlargement with no enlargement of the left atrium. The pulmonary artery segment was prominent, as were the hilar vessels, but the peripheral lung vasculature was thought to be normal or slightly decreased. A "hilar dance" was not thought to be present. An ECG (Fig. 1) showed right axis deviation with the pattern of right ventricular hypertrophy and strain. Pulmonary function studies (Table 1) were only slightly abnormal, and were not thought to indicate pulmonary disease of any severity.

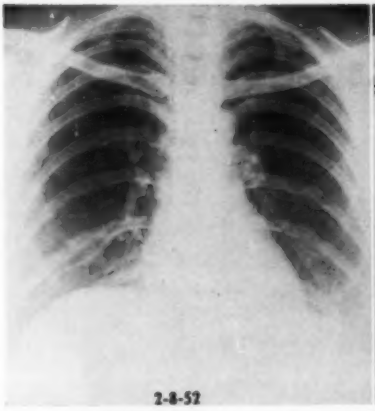

FIGURE 2

FIGURE 3

FIGURE 2: Chest x-ray films of February 8, 1952 reported normal. FIGURE 3: Chest x-ray film of March 21, 1955 showing early cardiac enlargement.

TABLE 2 — CATHETERIZATION DATA

Right Atrium, mean	15 mm. Hg.
Right ventricle	82/5-20
Pulmonary artery	78/32
Pulmonary artery, mean	54
Pulmonary capillary, "wedge"	2
Femoral artery	127/80
Femoral artery, mean	100
Cardiac output	2.6 L./min.
Pulmonary resistance	1800 dyne sec. cm.$^{-5}$

She was given digitalis, but showed no response whatsoever. She did become edema free on a low salt diet and occasional injections of mercurial diuretics. Her clinical status remained stable and she was readmitted for right heart catheterization on January 22, 1959. The physical findings and laboratory data were unchanged. The ECG (Fig. 1) showed a more pronounced right ventricular hypertrophy and strain pattern with the development of "P Pulmonale" P waves. The catheterization results are summarized in Table 2. No evidence of a left to right or right to left shunt was found and the pulmonary capillary "wedge" pressure was normal. Following the right heart catheterization, an open lung biopsy was performed. The patient tolerated the procedure well.

The pathologic report of the lung biopsy is in part as follows: "In the small arteries (Fig. 6 and 7) and in the arterioles (Fig. 8 and 9) there are profound changes with marked lumenal narrowing of these vessels due primarily to medial thickness, but with some fibrous intimal proliferation as well. The degree of lumenal narrowing is somewhat variable although virtually all of the small arteries and arterioles show an estimated 50 per cent diminution in lumenal size. Frequently this narrowing is so marked that small muscular arteries can accommodate only three to ten erythrocytes in their widest diameter. Except for the vascular narrowing and moderate emphysema, no other structual alterations are noted. There is no fibrosis or evidence of either recent or remote inflammation and no pigment laden macrophages are found within the alveoli."

Discussion

This case is similar to many that have been reported in detail in the literature, and there is no need to review the characteristic clinical and laboratory findings, or to comment on the results of the right heart catheterization. It is of interest, however, to point out the evolution of the ECG from normal in 1952, through the development

FIGURE 4

FIGURE 5

FIGURE 4: Chest x-ray film of March 29, 1957 showing further cardiac enlargement with beginning prominence of the pulmonary artery segment. FIGURE 5: Chest x-ray film of October 13, 1958 showing further cardiac enlargement with congestion of the hilar vessels but with relatively avascular peripheral lung fields.

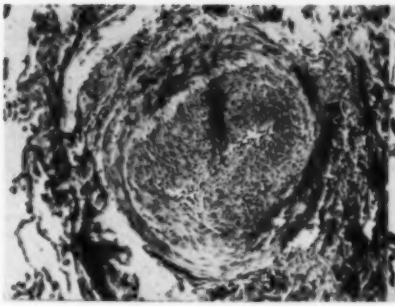

FIGURE 6

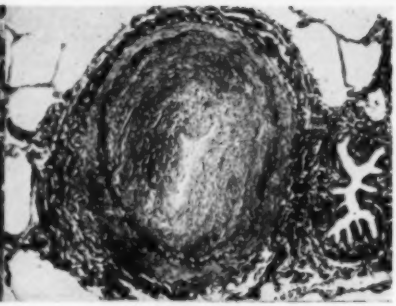

FIGURE 7

FIGURE 6: Photomicrograph of a small artery showing marked intimal proliferation.
FIGURE 7: Photomicrograph of a small artery stained with an elastic tissue stain showing the internal and external lamina. There is marked intimal proliferation with a very narrow lumen.

of early right ventricular strain, to right ventricular hypertrophy, and finally to the development of the classical "P Pulmonale" P waves of right atrial hypertrophy and dilatation. The serial chest x-ray films, while less striking, again show the gradual evolution of the increasing pulmonary vascular congestion with the development of right ventricular hypertrophy.

It is clear that this case represents acquired rather than congenital pulmonary hypertension. The possibility that this pulmonary hypertension was secondary to some other disease process was eliminated by pulmonary function studies and by right heart catheterization. With the other possibilities excluded, one is left with the diagnosis of acquired primary pulmonary hypertension. In discussing the etiology or pathogenesis of this disease, it is important to try to separate the congenital from the acquired form. This is not often done in the case reports in the literature. There are probably two reasons for this. The clinical picture is much the same whether the disease is found in a young infant, who presumably had the disease from birth, or in a young or middle-aged adult who must have acquired the disease. The pathologic picture is also rather non-specific and offers no distinguishing features between the congenital and the acquired form of the disease. The common lesions on pathologic examination of the lungs are pulmonary atherosclerosis and arteriolosclerosis, which are likely to be secondary to the hypertension, and hypertrophy of the media of the small arterioles.

Goodale and Thomas[15] found medial hypertrophy to be the predominant lesion in two cases of primary pulmonary hypertension in children seven months and ten years of age. They concluded that this change represented persistence of the thick walled fetal pulmonary arterioles. However, they also found medial hypertrophy of a similar degree in five cases of congenital heart disease, but felt that in this situation, the medial hypertrophy was a compensatory mechanism in response to the abnormally

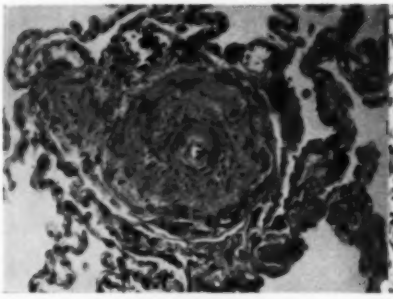

FIGURE 8

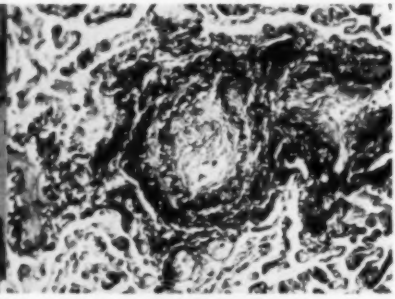

FIGURE 9

FIGURE 8: Photomicrograph of a pulmonary arteriole showing marked medial hypertrophy with very little intimal thickening. Note the minute lumen.
FIGURE 9: Photomicrograph of a pulmonary arteriole stained with elastic tissue stain showing reduplication of the elastic membrane with some medial hypertrophy and some proliferation of the intima.

large amount of blood flowing through the pulmonary vascular tree. They felt that the proliferation and fibrous thickening of the intima found in all varieties of pulmonary hypertension were secondary to the hypertension itself.

The varying degrees of inflammatory reaction that have been described in the pulmonary arterioles of patients with primary and secondary pulmonary hypertension[11,12,16,17] are probably also secondary reactions to the hypertension, as are the small thrombi that have been described in the arterioles.[13,14,17]

In the majority of the cases of acquired primary pulmonary hypertension in the literature, as in the present case, medial hypertrophy is a prominent pathologic finding. The hypothesis of persistence of the thick-walled fetal arterioles does not explain the pathologic picture found in these cases. There are reported cases that have been shown to have primary pulmonary hypertension during life who have no pathologic pulmonary vascular changes at post mortem examination.[18] The most satisfactory hypothesis to explain the varied pathologic picture is that proposed by Dresdale in 1951[8] and reaffirmed in 1954.[19] He suggested that the increased pressure was secondary to increase in the pulmonary vascular resistance caused by increased tone in the pre-capillary arterioles. He produced evidence that at least some of the pulmonary vascular resistance was vasospastic in nature by demonstrating a fall in pulmonary artery pressure with an increase in cardiac output after injection of Priscoline into the pulmonary artery of several patients with primary pulmonary hypertension.

Wood[1] also found a fall in pulmonary artery pressure in five of six patients with primary pulmonary hypertension when he injected 1 mg. of acetylcholine into the pulmonary artery. In fact, he found a greater response to acetylcholine in this condition than in any other type of pulmonary hypertension. He felt that this was good evidence that a significant degree of pulmonary vasoconstriction existed in primary pulmonary hypertension.

The situation may well be analogous to hypertension of the systemic circulation. The primary process may be an arteriolar vasoconstrictive response to some unknown stimuli, with the secondary development of varied pathologic lesions in different patients.

SUMMARY

A 42 year-old woman, observed since 1948 for a blood disorder, developed physical signs of pulmonary hypertension. The electrocardiogram changed from normal to right ventricular strain and hypertrophy while heart fluoroscopy showed increasing prominence of the pulmonary artery and right ventricle. Lung function studies were normal. Heart catheterization revealed a pulmonary artery pressure of 78/32 mm. Hg. and a pulmonary capillary pressure of 2 mm. Hg. The total pulmonary vascular resistance was 1800 dynes cm.$^{-5}$ secs. There was no evidence of intracardiac shunt. Lung biopsy showed marked medial hypertrophy of the arterioles plus modest intimal proliferation.

The cause of pulmonary hypertension in this case is not known, but it is clearly acquired. There is no evidence that the marked medial arteriolar hypertrophy is a consequence of previous vasospasm although a vasospastic element has been demonstrated in similar cases. Medial arteriolar hypertrophy occurs in both the congenital and acquired forms of primary pulmonary hypertension and hence is not a helpful differential diagnostic point.

RESUMEN

Una mujer de 42 años, observada desde 1948 con motivo de un padecimiento hemático, presentó signos de hipertensión pulmonar. El electrocardiograma cambió de normal a manifestaciones de esfuerzo ventricular derecho e hipertrofia en tanto que la fluoroscopia del corazón mostró prominencia creciente de la arteria pulmonar y del ventrículo derecho.

Los estudios de la función pulmonar dieron datos normales. La cateterización del corazón reveló presión de la arteria pulmonar de 78/32 mm. Hg. y la presión pulmonar capilar fué de 2 mm. Hg.

La resistencia vascular pulmonar total fué de 1800 dunas cm.$^{-5}$ segs. No hubo evidencia de intercomunicación de cavidades cardiacas.

La biopsia de pulmón señaló hipertrofia de la capa media de las arteriolas y ademas moderada proliferación de la íntima.

La causa de la hipertensión pulmonar en este caso no se conoce pero evidentemente es adquirida. No hay evidencia de que la hipertrofia de la media arteriolar sea consecuencia de espasmo previo aunque un elemento vasoespático se ha demostrado en casos similares.

La hipertrofia de la capa media arteriolar acontece tanto en las formas mas congénitas como en las adquiridas de la hipertensión pulmonar primaria y por tanto, no es una ayuda para el diagnóstico diferencial en este punto.

RESUMÉ

Une femme âgée de 42 ans, suivie depuis 1948 pour des troubles hématiques, a présenté des signes physiques d'hypertension pulmonaire. L'électrocardiogramme se modifia: d'abord normal il montra une fatigue ventriculaire droite et une hypertrophie tandis que la radioscopie cardiaque montrait une augmentation de la saillie de l'artère

pulmonaire et du normales. Le cathétérisme cardiaque révéla une pression de l'artère pulmonaire de 78/32 mm. de mercure et une pression des capillaires pulmonaires de 2 mm. de mercure. La résistance totale des vaisseaux pulmonaires fut de 1,800 dynes par cm.$^{-5}$ seconde. Il n'y eut aucune preuve de shunt intracardiaque. La biopsie pulmonaire montra une nette hypertrophie de la média des artérioles et une faible prolifération de l'intima.

La cause de l'hypertension pulmonaire dans ce cas n'a être décelée mais il s'agit certainement d'une affection acquise. Il n'y a aucune preuve que la nette hypertrophie de la média de l'artériole soit une conséquence du vasospasme antérieur, bien qu'un élément de spasme vasculaire ait été mis en évidence dans des cas semblables. Une hypertrophie de la média de l'artériole peut se voir aussi bien dans les formes congénitales que dans les formes acquises d'hypertension pulmoniare primaire et ne permet donc pas d'aider le diagnostic différentiel.

ZUSAMMENFASSUNG

Bei einer 42 Jahre alten Frau, die seit 1948 wegen Blutungs-störung unter Beobachtung stand, traten die physikalischen Zeichen einer pulmonalen Hypertension auf. Das Elektrokardiogramm veränderte sich von einem normalen Befund zu demjenigen einer Belastung und Hypertrophie des rechten Ventrikels, und die Röntgenuntersuchung des Herzens zeigte ein zunehmendes Hervortreten der art. pulm. und des rechten Ventrikels. Die Lungenfunktionsproben waren normal. Die Herzkatheterisierung ergab einen pulmonalen arteriellen Druck von 78/32 mm Hg und einen pulmonalen kapillaren Druck von 2 mm Hg. Der gesamte pulmonale Gefäßwiderstand betrug 1800 Dyn. cm.$^{-5}$ sec. Für einen intrakardialen Shund fand sich kein Anhaltspunkt. Die Lungenbiopsie zeigte eine ausgeprägte Hypertrophie der Media der Arteriolen und zusätzlich eine mässige Intima-Proliferation.

Die Ursache für den pulmonalen Hochdruck dieses Falles ist nicht bekannt, sie ist aber doch bestimmt eine erworbene. Es findet sich kein Anhalt dafür, daß die ausgeprägte Hypertrophie der Media der Arteriolen die Folge eines vorausgegangen Gefäßspasmus darstellt, obwohl ein vasospastisches Element in analogen Fällen nachkewiesen wurde. Media-Hypertrophie der Arteriolen tritt wohl in angeborenen wie in erworbenen primären pulmonalen Hypertensionfällen auf und läßt sich daher nicht bei differential-diagnostischen Erwägungen zu Hilfe nehmen.

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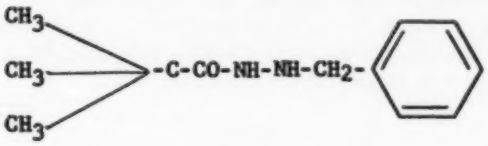
Tersavid®* (RO 4-1634), An Amine Oxidase Inhibitor, for the Treatment of Angina Pectoris**

Up to 15 Months Follow-up Study

The serendipitous discovery of iproniazid as an effective agent for the prevention and treatment of angina pectoris,[1] followed by a number of corroborating reports,[2] was a boon to the countless numbers suffering from this most agonizing and disabling ailment. It heralded a new era in medical therapeutics. However, since its use often was accompanied by some very unfavorable clinical reactions, a number of new monoamine oxidase inhibitors have been introduced with the aim of developing one that is not only effective as an antianginal agent, but is also of low toxicity. In our experience, the preparation used in this study appears to possess both these qualities. It is called "Tersavid®" (formerly Ro 4-1634), an analog of iproniazid (Marsilid®)*; the chemical formula is 1-benzyl-2-trimethyl-acetylhydrazine, with the following structural formula:



Material

Thirty-one patients, 18 men and 13 women, were followed for periods up to 15 months; age distribution ranged from 35 to 81 years. All of these subjects had angina pectoris. They gave typical histories of attacks of substernal pains and dyspnea following varying degrees of exertion. One had angina decubitus. The diagnosis of coronary disease was corroborated by a careful history and physical examination including the electrocardiogram. Most of these patients had been under our care for some time before they were started on Tersavid, and medication had consisted of the usual antianginal preparations: nitroglycerine, long-acting nitrites, and sedatives.

Dosage

Dosage was based on the patient's individual needs and reactions. This policy should be meticulously adhered to with the use of any therapeutic agent, but particularly with a compound in which the mode of action is not fully understood. Many of the serious toxic complications that occur

*Hoffman-La Roche Inc., Nutley 10, New Jersey.

**Presented before the meeting of the Sixth International Congress on Diseases of the Chest, Vienna, Austria, August 27, 1960.

during or following the use of potent drugs are usually due either to their indiscriminate use or adherence to a fixed schedule dosage.

It was not considered wise to attempt to prevent all angina by increased dosage of the drug. Without the forewarning of anginal pain a false sense of security could result in the patient's exertion to the point of danger. Patients were instructed to take one 25 mg. tablet for four days and one-half tablet each morning thereafter. The 12.5 mg. daily dosage has been the usual maintenance dose employed except for two patients of this group; one of these developed an orthostatic hypotension and is maintained adequately on 6.25 mg. daily, and the other, a physician, found his optimum dose to be 50 mg. taken in 2 divided doses.

Method of Evaluation

The measure of the therapeutic benefit was based on the number of nitroglycerine tablets needed daily by the patient, before and after the use of Tersavid, for carrying out the usual daily chores, the distance the patient was able to walk, and the amount of exertion he was capable of before precordial pain was experienced. Results were classified as good, fair, and poor. Results classified as good were those in which the anginal attacks were completely controlled or so markedly reduced that the patient could accomplish his or her daily activity in comfort. Results were classified as fair when the number and severity of the attacks were so diminished that one-half or less the usual number of nitroglycerin tablets were needed to carry on daily physical duties.

Liver function tests: cephalin flocculation, thymol turbidity, transaminase, alkaline phosphatase, and serum bilirubin were performed on 18 patients after 4 to 15 months of treatment.

Results

The results of therapy are exemplified by representative case histories. The clinical and laboratory results in 18 of the patients on whom liver function tests were done are summarized in Table 1.

Side Reactions

Untoward reactions were rare and consisted only of an orthostatic drop in blood pressure in two patients accompanied by a slight vertigo in one. The patient with vertigo was controlled by reducing the maintenance dose from 12.5 to 6.25 mg. In the other instance, the fall was insufficient to cause symptoms and the dosage was not changed.

There were no instances of jaundice, gastrointestinal disturbances, blood dyscrasias, syncope, or cardiographic changes. Although this is a relatively small group, it indicates that this drug in the dosage used is not toxic for the liver. Blood studies showed no abnormal changes in the hemoglobin, red blood cells, white blood cells, or hematocrit.

Case Histories

Cases Illustrative of the Category—Good.

1. An 81 year-old white woman was more or less confined to her apartment since an attack of myocardial infarction in 1948 because of severe precordial pains on the least exertion. For a year she could not walk to the corner drug store, one-quarter block down the street, without finding it necessary to stop once or more because of

dyspnea and chest pain. She often complained bitterly of being a confined, dependent invalid. On February 12, 1959, oral administration of Tersavid was started. A single dose of 25 mg. was given each morning for four days and 12.5 mg. thereafter. After a few weeks of therapy, she was able to walk five or six blocks without any discomfort. Recently she boasted that she not only could do her own marketing, some two and one-half blocks away from her apartment, but that she also had prepared and served a dinner for a party of eight without any precordial distress. In April of 1960, she left for Chicago, very exuberant and gay, to attend her granddaughter's wedding. Only occasionally has she a need for a nitroglycerin tablet.

2. A 77 year-old man could not walk more than two blocks without experiencing an attack of dyspnea and precordial pain. On February 13, 1959, therapy with Tersavid was started. Within a period of two weeks, he was able to walk several blocks without any sign of discomfort. Since June 29, 1959, the daily maintenance dose of the drug has been only 6.25 mg. per day, since side effects were noted on persistent dosage of 12.5 mg. per day. The side effects consisted of a slight vertigo, with an orthostatic drop in blood pressure of 30 mm. It is now over 15 months since he started with Tersavid, and over ten months since he has been on a maintenance dose of 6:25 mg. He has had no need for nitroglycerine. He recently was out for a walk, when he found himself lost. He said that he walked for more than three miles before he found his way back and "was surprised" that he had no discomfort other than fatigue.

A Case Illustrative of Category—Fair.

This 55 year-old white woman works in a department store. Since treatment with Tersavid she has noted that, although there has been no decrease in the number of anginal attacks, the threshhold for pain has increased. She can do more work before she experiences any angina, and the pains are much less severe.

Deaths

1. A diabetic woman, aged 76, had a history of angina and episodes of cardiac failure for ten years. She showed evidence of coronary sclerosis, left bundle branch block, and cardiac enlargement. She was started on Tersavid on May 1, 1959. The anginal attacks were well controlled, and the results of treatment were considered good. On November 6, 1959, she had an acute myocardial infarction and expired within two hours.

2. A woman, aged 77, had several attacks of angina since 1950 and had been in chronic congestive failure since January of 1960. Diagnoses included essential hypertension, hypertensive heart disease, and coronary sclerosis. Tersavid therapy was started on May 23, 1959. Results were considered good. On April 17, 1960, she had a massive posterior myocardial infarction with immediate shock. She expired in six hours.

3. A man, aged 73, had a history of anginal attacks for 25 years. He was under our care for coronary sclerosis and angina pectoris for ten years. Tersavid was started on March 10, 1960. The patient showed no improvement. He required nine to ten nitroglycerine tablets daily before and after therapy with Tersavid. On April 4, 1960, he had an acute myocardial infarction and died on April 6, 1960.

LIVER FUNCTION TESTS 4 TO 15 MONTHS FOLLOWING THE USE OF RO 4-4634 (TERSAVID*)

TERSAVID STARTED	CASE PT. SEX AGE	LAST TEST	CEPHALIN FLOCCULATION (4 DAYS — UNITS)	THYMOL TURBIDITY (UNITS)	TRANSAMINASE SGO-T (UNITS)	ALKALINE PHOSPHATASE (UNITS)	SERUM BILIRUBIN (mg. %)	CLINICAL RESULTS
2-12-59	F.B. ♀ 61 YRS.	5-13-60	NEG.	24	0.5	16	3.6	0.30	GOOD
2-13-59	H.R. ♂ 77	5-10-60	NEG.	24	0.3	18	4.3	0.30	GOOD
3-7-59	S.S. ♂ 59	6-4-60	NEG.	24	0.4	16	2.0	0.50	GOOD
3-30-59	J.M. ♂ 65	5-12-60	1+	24	0.5	20	1.6	0.45	GOOD
5-4-59	M.M. ♂ 70	5-12-60	1+	24	1.1	27	4.2	0.40	GOOD
5-6-59	W.H. ♂ 76	5-18-60	NEG.	24	0.1	12	1.8	0.40	GOOD
6-2-59	M.E. ♂ 60	5-19-60	NEG.	24	0.7	27	2.0	0.40	GOOD
6-10-59	R.S. ♀ 55	5-20-60	NEG.	24	0.5	18	1.9	.00	FAIR
7-9-59	H.R. ♂ 65	5-17-60	NEG.	24	0.8	21	2.0	0.30	FAIR
10-10-59	E.I. ♂ 57	5-14-60	NEG.	24	0.9	24	3.5	0.58	EXP. 5-15-60 FOLLOWING ACUTE MASSIVE CORONARY OCCLUSION
10-22-59	G.A. ♀ 67	5-19-60	NEG.	24	0.4	28	2.6	0.20	GOOD
10-23-59	L.A. ♂ 48	5-14-60	NEG.	24	0.8	10	2.0	0.45	FAIR
11-7-59	L.C. ♀ 73	5-10-60	NEG.	24	0.8	19	2.8	0.30	GOOD
11-10-59	R.S. ♂ 47	5-10-60	NEG.	24	1.0	16	2.1	0.40	GOOD
11-12-59	M.M. ♀ 67	5-11-60	NEG.	24	0.8	24	1.7	0.20	POOR
11-17-59	C.S. ♀ 61	5-10-60	1+	24	1.2	11	2.8	0.20	GOOD
12-28-59	S.H. ♂ 63	5-11-60	NEG.	24	0.6	15	2.0	0.27	FAIR
1-8-60	L.M. ♂ 70	5-11-60	NEG.	24	0.8	18	2.7	0.35	GOOD

*ROCHE

TABLE 1

It is not our impression that Tersavid was a contributing factor in these three deaths. However, there is the remote possibility that these patients had periods of marked hypotension which could have been, according to Master, Dack, and Jaffe,[3] a contributing factor in the myocardial infarction. During examinations, none of the three patients had demonstrable periods of hypotension. The ages of these patients and the long histories of cardiac disease certainly allow for death without iatrogenic contribution.

Mode of Action

The mode of action of Tersavid has not yet been elucidated. However, several theories have been advanced. It is fairly well established that angina pectoris results from physiological imbalance between the myocardial need for oxygen and the satisfaction of that need. Reduction in coronary arterial flow, due to functional or organic changes in the coronary vessels, is usually the underlying factor. Furthermore, various types of cardiac disease, including myocardial infarction, congestive heart failure, cardiac hypertrophy, myocardial degeneration and coronary sclerosis have been shown to be associated, in many instances at least, with an augmented myocardial catecholamine content particularly epinephrine;[4] and epinephrine has been demonstrated to be a potent "oxygen waster."[5] Since there is evidence that MAO inhibitors have an oxygen sparing effect,[6] one is tempted to explain the anti-anginal effect of these drugs on this basis.

Although a transient increase in coronary flow can be demonstrated in animals following intravenous administration of several MAO inhibitors,[7] Zbinden[8] has judged this mechanism to be most unlikely after chronic oral use of these drugs in man. Pletscher and Bernstein[9] have called attention to an increase in the serotonin content of the blood in human subjects following the taking of MAO inhibitors. It has been theorized that this substance, shown to have coronary dilator properties,[10] may contribute to the salutary effect of iproniazid and other monamine oxidase inhibitors on anginal pain. Finally psychostimulation[2d] and blocking effects on pain transmission have been advanced as possible mechanisms. Much is yet to be learned about the pharmacologic actions of these various MAO inhibitors. One cannot be certain that amine oxidase is the only or even the most important enzyme inhibited.

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SUBCLINICAL RHEUMATIC CARDITIS

In a series of 175 biopsy specimens of left atrial appendages from mitral valvotomy operations, active histologic lesions were found in 112 (64 per cent). In a necropsy series of comparable age and comparable valve lesions, the total incidence of active lesions in the heart was 24 per cent.

No correlation was found between the usual clinical criteria of rheumatic activity and the presence of histologically active lesions. Since the earliest forms of rheumatic lesions were found in some specimens in the absence of clinical evidence of rheumatic activity, it is deduced that rheumatic carditis can be subclinical.

A large difference in the incidence of active lesions was found in patients in sinus rhythm and in atrial fibrillation in the biopsy series and to a lesser extent in the necropsy series. It is suggested that the different proportions of patients in sinus rhythm in biopsy and necropsy series may account in part for the difference in incidence of active lesions in most biopsy and necropsy series. The explanation for the low incidence of active lesions is atrial fibrillation has not been found, but it is suggested that the conditions leading to the development of atrial fibrillation are associated with the healed rheumatic process.

In view of the frequent occurrence of subclinical rheumatism it is suggested that prophylactic or suppressive measures should be continued throughout life.

Lannigan, R.: "Subclinical Rheumatic Carditis," *Brit. Heart J.*, 23:35, 1961.

EFFECTS OF SYNTHETIC ANGIOTENSIN AND NORADRENALINE ON BLOOD PRESSURE AND RENAL FUNCTION

The effects of synthetic angiotensin II on blood pressure and renal function have been investigated in a group of normal subjects and compared with those of noradrenaline. Angiotensin proved considerably more potent in raising blood pressure, but was associated with a greater depression of renal function. On the other hand, venospasm was less marked with angiotensin than with noradrenaline.

Synthetic angiotensin II deserves further study for its use in hypotension. The decrease in renal function found in subjects with a normal pressure will require evaluation.

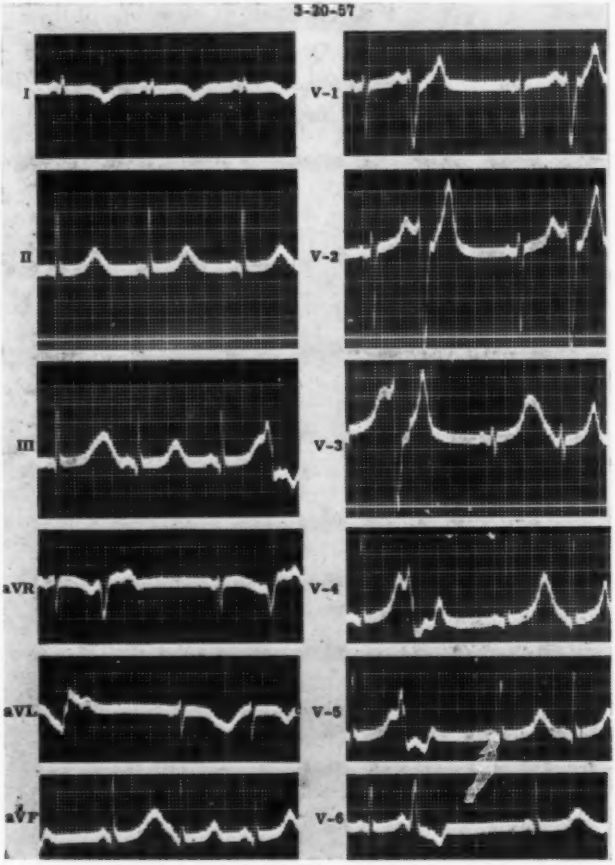
McQueen, E. G., and Morrison, R. B. I.: "Effects of Synthetic Angiotensin and Noradrenaline on Blood Pressure and Renal Function," *Brit. Heart J.*, 23:1, 1961.

ELECTROCARDIOGRAM OF THE MONTH

Electrocardiographic Clues in the Diagnosis of Syncope

Edited by Stephen R. Elek, M.D.

A 36 year-old housewife was referred to the Mayo Clinic because of "fainting spells" during the preceding four months. She often had an aura of "rising sensation" in the anterior portion of the chest prior to unconsciousness which lasted from a few seconds to 5 minutes. The patient's husband had noticed that her head would turn to the left and backward, that breathing was stertorous and that the right arm and hand would twitch occasionally. On regaining consciousness she was confused temporarily and frequently had a mild frontal headache. The spells generally occurred in the evening while she was sitting down or



FIGUURE 1

lying supine. In some instances they were aborted by deep inspiration or by being lifted to a sitting position. The syncopal attacks had been especially frequent in the two weeks preceding examination. The patient gave a remote history of four or five transient fainting spells between the ages of 18 and 24 years, which she had attributed to emotional stress. She had been aware also of occasional palpitations in the previous two years.

On examination the blood pressure was 150 mm. of mercury systolic and 100 mm. diastolic, and the pulse rate was 80 beats per minute. Massage of the carotid sinuses did not produce unusual bradycardia or syncope. Hyperventilation for three minutes was associated with only mild light-headedness. With the exception of an occasional premature systole, no cardiac abnormality was noted during the physical examination. Ophthalmoscopic examination revealed normal fundi, and neurologic evaluation disclosed no abnormalities.

The following laboratory studies gave normal results: hemoglobin, erythrocytes, leukocytes, sedimentation rate, fasting blood sugar, serum calcium and serum phosphorus. The serologic test for syphilis was nonreactive. Roentgenograms of the head and thorax and an electroencephalogram showed normal conditions.

A resting electrocardiogram (Fig. 1) revealed a cardiac rate of 63 beats per minute accompanied by multiple ventricular premature contractions. Bizarre T waves were noted; they were inverted in leads I and aVL and were broad and abnormally positive in several of the other leads. The Q-T interval varied from 0.46 to 0.68 second in the sinus-controlled beats, whereas in the ventricular premature systoles, the Q-T interval was approximately 0.40 second.

The unusual electrocardiographic features suggested a cardiac basis for the attacks; the differential diagnosis rested between cardiac standstill and ventricular fibrillation. In an attempt to obtain an electrocardiogram during one of the attacks, the patient was admitted to the hospital.

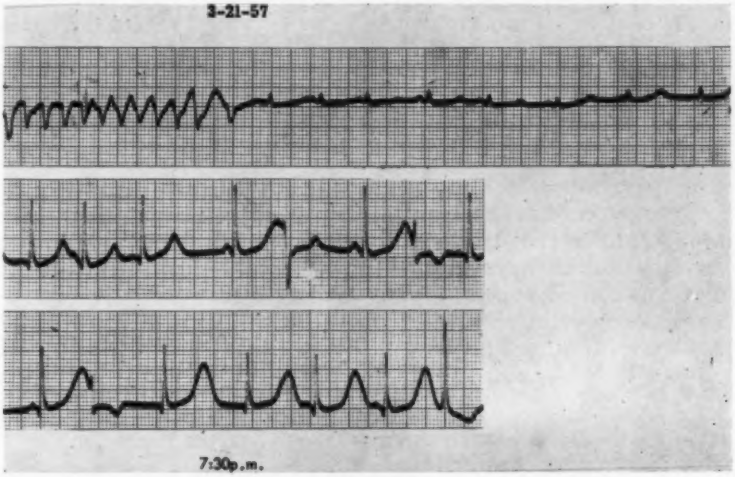


FIGURE 2

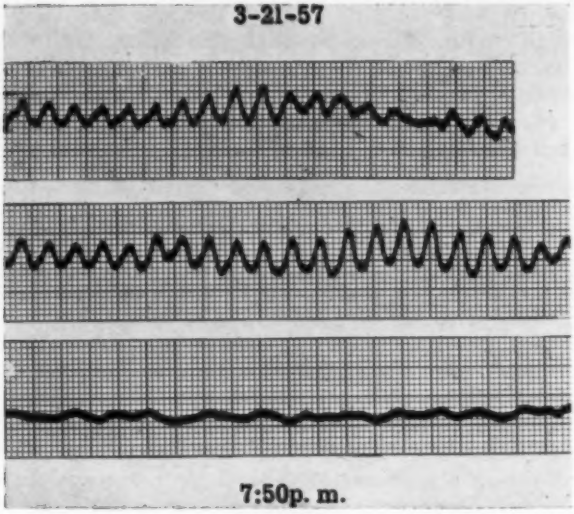


FIGURE 3

At 7 o'clock on the evening of admission a control electrocardiogram was taken which was essentially the same as that shown in Figure 1. At 7:30 p.m. she had a brief fainting spell during which the electrocardiogram showed a brief run of ventricular tachycardia (Fig. 2), but the pattern reverted quickly to that in the previous control tracing. The electrocardiographic electrodes were left attached. At 7:50 p.m. the patient was found unconscious, cyanotic, and apneic; no heart sounds were audible. Ventricular fibrillation was recorded in the electrocardiogram (Fig. 3). The chest was pounded and artificial respiration was instituted; procaine amide hydrochloride (Pronestyl) was given, and intracardiac administration of epinephrine was carried out, but she failed to respond.

Clinically, an underlying diffuse myocardial disorder was suspected from the control electrocardiogram (Fig. 1) which reflected a delay in the recovery phase with marked prolongation of the Q-T interval and the unusual abnormalities of the T waves. The multiple ventricular premature systoles were, in retrospect, an omen of the otherwise unexpected terminal ventricular fibrillation.

At necropsy, the heart weighed 290 gm., and no gross abnormalities were noted. However, histopathologic examination disclosed patchy areas of necrotic myocardial fibers and lymphocytic infiltration consistent with acute myocarditis of indeterminate origin. In addition chronic or healed myocarditis was manifested by areas of myocardial deficit and slight fibrosis. The coronary arteries were considered normal.

The patient's course also exemplifies the hazard of mechanism death in patients with diffuse myocarditis.

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Editorial

The Mutations of *M. Tuberculosis*

Sometimes we become so engrossed in our specialized duties that we are unable to view the larger workings of nature; we fail to see the forest for the trees. This may apply to the question of mutation and its bearing on the understanding and management of tuberculosis. To take a larger view of our problems with *Mycobacterium tuberculosis,* or at least a different view, we must look over the shoulders of the geneticists, bacteriologists and biochemists, who are giving us new ways of understanding tubercle bacilli and the changes that take place in them.

For some time after the discovery of the tubercle bacillus, scientists regarded it as a rather constant bacillary form having rather rigid tinctorial and growth characteristics. Especially was this true of Koch and Cohnheim who are considered the leaders of the school of "monomorphism" of bacteria. Within a few years after the discovery of the bacillus, the avian strain was isolated by Maffucci and the bovine strain by Theobald Smith. Since then, many acid-fast bacilli have been found in cold-blooded animals. More recently in England a bacillus has been found in voles.

Although changes in morphology of the human bacillus as reported by Metchnikoff, Spengler, Much, and others, were only of academic interest, changes in the growth of the bacillus and the appearance of aberrant or related forms began finally to arouse a more practical interest. For example, Corper in 1918 found, out of one hundred strains of tubercle bacilli cultured from sputum, three were not virulent for guinea pigs. This was perhaps the first indication that virulence for guinea pigs is not always present. Later, A. Stanley Griffith in England noted that bacilli isolated from skin lesions differed from typical forms. They seemed to resemble more the avian form in both appearance and characteristics. Still later Petroff, culturing tubercle bacilli on plates, found that two different types occurred according to colony morphology. The more virulent type was smooth; the other, a rough type, was generally avirulent. DeKruif called this phenomenon dissociation.

The present writer, with access to masses of material over a period of more than 20 years, made observations on both morphological and growth characteristics, anticipating discoveries of chromogens, phage activity, L-forms, and other peculiarities, some of which have been found and described more recently in bacteriological studies as mutants. These forms are not to be confused with the large group of acid-fast bacilli which are either parasites in cold-blooded animals or saprophytic forms. They seem rather to be the result of spontaneous changes in human tubercle bacilli in apparently normal environments.

Runyon has arranged atypical acid-fast bacilli into three groups, but new variants are being discovered constantly. Most of these variants are not sufficiently different from the norm to be classified as true variants, let alone separate species. Many are associated in the granulomatous disease similar or identical with what we have always called tuberculosis.

After the advent of antibiotics, changes in the bacillus were noted more frequently. One of the first indications of the appearance of mutants following drug treatment was the development of streptomycin-resistant strains after a few weeks of treatment. Similar observations were later made when PAS and INH came into use. Resistance appeared much earlier in the case of INH treatment than on treatment with the other drugs. In addition, many of the bacilli were found to be avirulent or only partially virulent for guinea pigs.

Other aberrations were also noted. Variations in reactions to many chemicals, such as thioglycollate, niacin, and neutral red, and the presence of certain enzymes like catalase and peroxidase were noted and studied. Many of these reactions could be used to distinguish the atypical forms from the typical forms. Various "atypicals," "anonymous," or "unclassified" bacilli, as they have been called by different authors, were being isolated in different parts of the United States; for example, *M. Kansasii* in Kansas and the "Battey" bacillus in Georgia. Similar atypicals have been studied in the Chicago area, in Florida, and elsewhere. This is probably a universal phenomenon.

It seems probable that most of these aberrant forms are the results of mutations, changes in the genetic material which are reflected in certain inheritable differences of form and function. The increase in mutant strains of the tubercle bacillus is confronting us with immediate practical problems in the treatment of tuberculosis. The most pressing of these is the problem of what to do about drug-resistant bacilli. We have developed certain techniques for minimizing the increase in resistance. We have learned that we must give drugs in large enough dosages to effect a cure before resistant forms can develop. We have learned that we can give drugs in combination, which reduces the likelihood that resistant bacilli will develop. We have learned that auxiliary treatment and public health follow-up must be thorough enough so that patients with resistant forms of the bacillus do not later spread these forms to other people.

But these measures do not solve the problem. Until we understand more about the exact mechanism of mutation and natural selection in the bacterial populations, we will not be able to develop the best means of solving these unknowns. For answers we must turn more and more, in the future, to the geneticists, bacteriologists, and biochemists who are studying this and similar problems with their own technical and conceptual tools.

The mechanism of mutation is essentially no different in tubercle bacilli than in any other form of life. Of course, there are several kinds of mutations. Some occur as the result of relatively large-scale changes in the genetic material, as when a piece of a chromosome is lost or destroyed. Others occur as the result of more subtle changes within the structure of the genetic material. It is the latter changes which biochemists are helping us to understand more clearly.

In recent years we have been provided with a remarkable theoretical model of the genetic structure of living things, and an explanation of what happens to it in mutation. The hypothetical genes of the chromosomes, the determiners of structural growth and functional characteris-

tics, are made up of ribose and desoxyribose joined with phosphorus and four (or five) amino acids to form ribonucleic acid (RNA) or desoxyribonucleic acid (DNA). The genes have been shown by biochemical methods and the Watson-Crick x-ray technique to consist of a flat ribbon-like structure arranged around a helix in millions of coils. The genes are thus made up of super-giant molecules. The outside of the ribbon structure is a chain of RNA or DNA groups with a phosphoric group in between each. In the center of this massive chain are located groups of the four amino acids, adanine, guanine, thymine, and cytosine. They are arranged in certain patterns, and these patterns correspond, in a way not yet explained, to all the inheritable characteristics of an organism. That is, it is the way that these groups are arranged which seems to determine the genetic characteristics. Although the basic units are few, the possibilities arising from different combinations of them are almost infinite in number. Hence the vast number and kinds of living things and the variations possible in any kind are not so surprising as they might seem at first. The giant molecule for each species has its own characteristic general structure. And, of course, the molecule for each individual within the species has its own individual structure.

Normally this complex giant molecule is surprisingly stable. During normal cell division the ribbon-like structure reproduces itself exactly, then splits into two exactly equal parts. Each of the two equal parts acts as a "director" to bring about the building of a new cell exactly like the original.

If this complex chemical were completely stable, of course, no evolution would have ever taken place. However, spontaneous changes do take place in the chemical structure of the molecule. Then the change in the genetic structure is perpetuated, and the offspring of the cell are different in some way.

Of course, the process of the evolution of new strains does not stop with the appearance of new individuals through mutation. Whether a given mutant survives, reproduces, and gives rise to a population like itself depends on the nature of the mutation and on the organism's relation to its total environment. Probably, we see only a small percentage of the mutants which arise in any bacterial population, because many of them are destroyed as soon as they appear or shortly thereafter. Only when they succeed in reproducing to the point where we can observe them, and only if their differences make them observably distinct from the norm do we become aware of them.

In ordinary circumstances, the normal forms of tubercle bacilli vastly outnumber the variant or mutant forms in any population and will overgrow them. This is easy to understand, since mutation occurs only once in many thousand to millions of organisms. However, a mutant may overgrow the normal form if for any reason it is better adapted to the environment, for example, if it is more resistant to human body defenses. This may account for the appearance of the photochromogens, scotochromogens, non-chromogens and other variants.

In the case of drug-resistant forms the factor of natural, really "artificial," selection is clearly seen. When a drug like isoniazid acts upon tubercle bacilli for the first time, the great mass of normal cells are

affected and their growth is stopped. The antibiotic seems to act like a key that locks the door of their metabolism. However, the mutant organisms which arise once in many thousands of cells have a chemical lock which is slightly different. The key does not fit; the mutant is able to grow and reproduce, and it gives rise to a variant strain, in this case, one that is resistant to the drug.

The incidence of mutation has been ably determined by Cohn, Middlebrook, and Russell for the three principal drugs used in tuberculosis treatment. They reported that one mutant resistant for INH occurred in approximately one hundred thousand cells; for streptomycin one in one million cells; and for the two drugs given together one in ten billion cells. If the sensitive forms are not suppressed, it is obvious that mutant forms may develop for any drug and any combination of drugs.

We know that drug treatment is, by natural ("artificial") selection, increasing the numbers of such a mutant population. But another important question remains to be answered. Is exposure to antibiotics actually increasing the rate of mutation itself? Is it responsible not only for the thriving of certain mutant forms, but also for the increased production of mutations? To answer this question we must understand more than we do at present about the cause of mutation.

Normally, all other things being equal, mutation tends to occur at a certain rate for any species. The cause is not known, but cosmic rays and the various influences of heat and cold are now assumed to play a role. Certain things are known to alter this rate of mutation; for example, radium emanation, and x-ray radiation greatly speeds up the rate of mutational changes. Ultraviolet light has also caused an increase. Certain chemicals have been found to do the same thing. There is reason to believe that antibiotics may be among the substances which actually increase the rate of mutation, but it still remains to be proved.

Many questions remain to be answered before we understand this problem. Is the exposure to drugs increasing the rate of mutation in the population as a whole? Or is it increasing the rate of mutation only in these strains which are resistant to drugs? Or are these forms genetically less stable than the normal population, hence more susceptible to all kinds of mutations? Or is it due to killing off the normals, leaving the atypicals to replace them?

Of course, we must do everything we can to apply what we do know about thorough treatment, good follow-up, and combined use of drugs. But more than this, we must begin to pursue the problem with all the research weapons available. The new atomic indicators, such as carbon-14, phosphorus-32, and nitrogen-15 may be used to trace the changes that take place during mutation. Other studies may be aided by x-ray stimulation and chemical irritation. We must be alert to the developments in sciences which may seem far removed from our immediate concerns with *Mycobacterium tuberculosis*, for it is these sciences which will ultimately give us the knowledge which will help us understand and ultimately solve the pressing problems.

HENRY C. SWEANY, M.D., F.C.C.P.
Mt. Vernon, Missouri

The President's Page

EMPIRICISM — DISCOVERY — RESEARCH

It is with amazement and with reverence that one contemplates sensible medical attainments of ancient days when determinant principles of science were nonexistent. Consequently, therapeutic methods of early practitioners of the healing arts were arrived at by trial and error. This, of course, renders their achievements even more startling and prompts one to ask if it be permissible to dignify these primitive gropings in the darkness of ignorance with the term, research. Perhaps so, if we accept the definition of B. Greenberg: "research is a burning yearning for learning."

For a great many centuries, empiricism prevailed in the Orient, Greece, the Roman Empire and in Arabic medicine until western civilization broke down the obstructive walls of scholasticism. The beginning of this era was signalized by arduous studies of pioneer anatomists and physiologists which were followed by an avalanche of scientific information in the fields of pathology and other branches of medicine.

The meticulous research work of Pasteur, Bordet, Gengou, Behring and Ehrlich, classics in their respective categories, set into motion an incessant flow of new knowledge, keen interest and intense enthusiasm. Even so, balanced against the pressing challenge of a great many diseases which hitherto have not been etiologically identified, successfully prevented, or treated, scientific progress seems to be *too slow*.

Scientific progress must not be left to serendipity. Advancement in science should be engineered within the framework of well organized and adequately financed research.

Let us take stock of our assets. The essential requirements for doing worthwhile research are: 1) persons who are qualified to do it; 2) technological and physical facilities; 3) purposefully arranged cooperative opportunities; 4) funds. For reasons too many to enumerate, independent, individual, unsponsored research is still going on. As a matter of fact, some very significant contributions to science have originated from such sources. Laudable as it is, this is far from being an ideal design. "Splintered" research is likely to entail much waste of money, talent, time and effort.

The same assets could be pooled in groups constituted for the explicit purpose of specific investigative studies. Medical schools, clinics, institutes, foundations and the pharmaceutical industry have taken prominent parts in establishing suitable opportunities. Moreover, the National Institutes of Health, the National Cancer Institute and other health units of the Federal Government have contributed in a praiseworthy manner to this endeavor.

I wonder how many doctors know that U. S. Government research expenditures are currently at the annual rate of 400 million dollars and that the Congressional Advisory Committee recommended a 264 million dollar increase this year.

The active, pertinent interest of the American College of Chest Physicians is well illustrated by its Council on Pulmonary Research and Council on Cardiovascular Research, by its respective international committees, 25 in number, as well as by its close relationship with the Research and Education Foundation for Chest Disease.

All this being so, moral encouragement and financial support of medical research are obligations which the medical profession and the public must not shirk.

27th ANNUAL MEETING
COMMODORE HOTEL — NEW YORK CITY
June 22 - 26, 1961

Fireside Conferences, one of the most popular features of the College meetings, will be held on Monday evening, June 26, in New York City, as part of the joint program of the American Medical Association and the American College of Chest Physicians. Eminent authorities will discuss various aspects of 36 cardiovascular and pulmonary diseases. All physicians are invited to participate in these informal discussions. The conferences pictured above were held at the College meeting in Miami Beach in June, 1960.

CHAPTER NEWS

Central Colombia Chapter

The Central Colombia Chapter was officially organized at a meeting in Bogota on August 24, 1960. Arrangements for the meeting were made by Dr. Carlos Arboleda Diaz, Regent, and Dr. Sigfrido Demner, Governor of the College for Central Colombia. The following scientific program was presented:

Aortic Stenosis
Jorge Pineros Bernal, Bogota

Esophagectomies Performed in the San Juan de Dios Hospital
Javier Llanos, Bogota

Oral Endoscopic Procedures
Gilberto Rueda Perez, Bogota

Dr. Demner spoke briefly on the aims and objectives of the College, after which the following chapter officers were elected:

President	Alfredo Artunduaga, Bogota
Vice President	Jose Rojas Franky, Bogota
Secretary-Treasurer	Miguel Ignacio Tobar-Acosta, Bogota

A second meeting of the chapter was held in Bogota on November 18.

Florida Chapter

The annual meeting of the Florida Chapter will be held at the Americana Hotel, Bal Harbour, Saturday, May 27, at which time the following program will be presented:

12:30 p.m. Luncheon and business session

2:00 p.m. Remarks
M. Jay Flipse, Miami, President of the College
Abnormal Mechanics of Breathing
Asher Marks, Miami
Physiologic Approach to Respiratory Failure
David M. Travis, Boston, Massachusetts
Surgical Aspects of Emphysema
Richard G. Connar, Tampa
Medical Evaluation and Management of Pulmonary Emphysema
Herbert O. Sieker, Durham, North Carolina
Discussion by panel and from the floor

Georgia Chapter

The Georgia Chapter's annual meeting will be held in Atlanta, May 8, in conjunction with the meeting of the Georgia Medical Association. The chapter will present the following program:

11:00 a.m. Pulmonary Diseases Due to Air Pollution
Andrew L. Banyai, Chicago

12:00 noon Business Luncheon

The Sections on Medicine, Radiology and Chest Diseases will present a joint meeting, as follows:

2:30 p.m. Claude F. McCuiston, Atlanta, presiding
Patterns of Histoplasmosis
Sol Katz, Washington, D. C.
An Objective Appraisal of Some Patients with Congenital Intracardiac Defects Who Have Had Open Heart Surgery
Robert H. Franch, Atlanta
Surgical Treatment of Isolated Pulmonary and Infundibular Stenosis, Using Extracorporeal Circulation
Richard King, James B. Minor, William A. Hopkins, M. Bedford Davis, Jr., William C. Wansker and Lester Rumble, Jr., Atlanta
A Study of 500 Cases of Carcinoma of the Lung
Osler A. Abbott, William E. Van Fleit and Michael F. Sawwan, Atlanta
Pathogenesis and Treatment of Pulmonary Emphysema
Andrew L. Banyai, Chicago
Panel discussion: Chest Disease
Moderator: Ross L. McLean, Atlanta; Panelists: Osler A. Abbott, Atlanta; Andrew L. Banyai, Chicago; Robert E. Wise, Boston

Japan Chapter

Members of the Japan Chapter attending meeting in Nagoya, October 30, 1960.

More than 300 members attended the fall meeting of the Japan Chapter of the College in Nagoya on October 30. The scientific session was devoted to symposia on Carcinoma of the Lung, Treatment of Pulmonary Suppuration, Chemotherapy of Pulmonary Tuberculosis, and Heart Surgery.

Illinois Chapter

The annual meeting of the Illinois Chapter, to be held at the Sherman Hotel, Chicago, May 15, will consist of the following Fireside Conferences starting at 8:00 p.m.:

Pediatric Cardiology—Maurice Lev, Moderator
Thomas G. Baffes, Donald E. Cassels, Joseph R. Christian, Benjamin M. Gasul, Bessie L. Lendrum, Milton Weinberg, Jr.

Thoracic Emergencies—Jerome R. Head, Moderator
Ward H. Eastman, Kenneth C. Johnston, John L. Keeley, William M. Lees, Max S. Sadove, Earl B. Sanborn, Darrell H. Trumpe

Congestive Heart Failure—Aldo A. Luisada, Moderator
V. Thomas Austin, Harry A. Bliss, Theodore Z. Polley, John T. Sharp, Gerry A. Smyth and Hugh A. Flack

Acute Myocardial Infarction—William H. Phelan, Moderator
Richard J. Jones, Paul Kezdi, Virgil C. Keeling, Chauncey C. Maher, Edward J. O'Donovan, Jakub G. Schlichter

Chemotherapy and Tuberculosis—Karl H. Pfuetze, Moderator
LeRoy Berard, Kenneth G. Bulley, Thomas W. Lester, Jr., Meyer R. Lichtenstein, David F. Loewen, Charles K. Petter

Pulmonary Emphysema—Robert W. Carton, Moderator
George S. Berg, James H. Head, Morris A. Kaplan, Gordon L. Snider, Leon Unger, Quentin D. Young

Asymptomatic Lung Disease—David B. Radner, Moderator
Abel Froman, Samuel A. Levinson, David Reisner, Hildegarde A. Schorsch

Cardiac Surgery—Egbert H. Fell, Moderator
Houck E. Bolton, Arthur DeBoer, Ormond C. Julian, F. John Lewis, Peter V. Moulder, Laurence H. Rubenstein

Occupational Diseases of the Chest—Andrew L. Banyai, Moderator
Isadore Pilot, Oscar A. Sander, Eugene L. Walsh, John R. Winston

Pericardial and Pleural Diseases—Stanford K. Sweany, Moderator
William B. Buckingham, Harry J. Isaacs, William F. Kellow, Albert H. Niden, Raleigh C. Oldfield, Jr.

Cancer of the Lung—William E. Adams, Moderator
Reynold J. Gottlieb, Irving M. Greenberg, Paul H. Holinger, George W. Holmes, Robert J. Jensik, S. Allen Mackler, J. Robert Thompson

Nontuberculous Pulmonary Infections—Mark H. Lepper, Moderator
John J. Brosnan, Theodore R. Hudson, John H. Huss, A. Edward Livingston, Eugene T. McEnery, Irving Mack, Robert S. Mendelsohn

Pulmonary Function Testing—Albert H. Andrews, Moderator
David W. Cugell, Robert T. Fox, Burgess L. Gordon, Ross C. Kory, Edwin R. Levine, John F. Perkins, Jr.

Home Treatment of Tuberculosis—Edward A. Piszczek, Moderator
Clifton F. Hall, Louis J. Miller, Dan Morse, Julius B. Novak, Joseph Taymor, George C. Turner

Hong Kong and Macau Chapter

New officers of the Hong Kong and Macau Chapter, elected in December, 1960, are:

President	Phyllis Haddow, Hong Kong
Vice President	Hee Chee Chan, Hong Kong
Secretary-Treasurer	Stephen D. Sturton, Hong Kong

Minnesota Chapter

The Minnesota Chapter will hold its annual meeting at the Hotel Lowry, St. Paul, Sunday, May 21, at which time the following program will be presented:

1:00 p.m. Registration

2:00 p.m. Panel discussion—Emphysema, Moderator: Arthur M. Olsen

Panelists: Cyrus G. Brown, Jr., Medical Treatment; Coleman Connolly, Surgical Treatment; William Fifer, Diagnosis; Harold O. Peterson, X-ray Aspects; R. S. Rossing, Cardiopulmonary Physiology

Panel discussion—Cor Pulmonale, Moderator: John F. Briggs

Panelists: Howard Burchell, ECG Aspects; Lewis Carey, X-ray Aspects; Jesse Edward, Pathology; Arthur E. Kirkhoff, Treatment; William Martin, Diagnosis

4:00 p.m. Business meeting

5:00 p.m. Social hour

7:00 p.m. Dinner

Wisconsin Chapter

The Wisconsin Chapter will present a two-day scientific meeting in Milwaukee, May 2 and 3. On May 2, the chapter, together with the Wisconsin Society of Internal Medicine, will present the following program at Plankinton Hall, Milwaukee Auditorium:

2:00 p.m. Sarcoidosis
Harold Israel, Philadelphia
Management of Atelectasis in Bronchial Asthma
David B. Radner, Chicago
Pleurisy with Effusion
David T. Carr, Rochester, Minnesota
Panel discussion: Pleural Disease
Moderator: David T. Carr, Panelists: Helen A. Dickie, Madison; Harold Israel; Ben R. Lawton, Marshfield; David B. Radner; Donald Stevenson, Madison

The chapter's annual dinner and business meeting will be held at the Schroeder Hotel on May 2, 5 to 8 p.m. The panel discussion, "Obstructive Diseases of the Lung" with the following panelists will be presented during the dinner: Moderator, Jonn Rankin, Madison; Panelists: Hollis G. Boren, Houston, Texas; David T. Carr, Harold Israel and David B. Radner. Following the dinner, the chapter will present the following Fireside Conferences:

Cardiac Arrhythmias—Howard L. Correll, Sydney T. Gettelman, Nathan Grossman
Pleural Disease—William J. Blake, David T. Carr, Philip P. Feingold, Donald E. Koepke
Pulmonary Manifestations of Systemic Disease—Helen A. Dickie, Harold Israel, Julius M. Meyer
Bronchial Asthma—John A. Arkins, David B. Radner, A. J. Sosman, John R. Talbot
Pulmonary Emphysema—Edna M. Cree, Leon H. Hirsh, Nola M. Moore, Walter H. Thiede
Cardiovascular Surgery—William J. Gallen, Albert H. Pemberton, William P. Young
X-ray Diagnosis of Lung Disease—Richard P. Jahn, John H. Juhl, George H. Jurgens, Jerome L. Marks, Charles Schmidt
Occupational Lung Disease—Elston L. Belknap, Oscar A. Sander, Paul J. Whitaker
Treatment of Pulmonary Infections—John H. Flinn, Harold Rose, Burton A. Waisbren
Special Methods for Diagnosis and Study of Lung Disease—Hollis G. Boren, Francis B. Landis, John T. Pellett
Cardiac Rehabilitation—Robin N. Allin, William V. Baker, Robert W. Boyle, George A. Hellmuth

On May 3 at Engleman Hall, Milwaukee Auditorium, the chapter and the Wisconsin Society of Internal Medicine will sponsor the following program:

9:00 a.m. Ross C. Kory, Milwaukee, moderator
Hairspray Pneumonitis
R. C. Buxbaum, Madison
Cavitary Pulmonary Disease following Emboli
Allen Kind, Marshfield
Panel discussion—Pulmonary Embolism and Infarction
Moderator: Harold Israel; Panel: David T. Carr, David B. Radner, James M. Sullivan, Milwaukee
Etiology and Pathogenesis of Pulmonary Emphysema
Hollis G. Boren, Houston, Texas
Diagnosis of Localized Pulmonary Disease (case presentations)
Moderator: John Rankin; Panel: Hollis G. Boren, David T. Carr, Harold Israel, Walter H. Jaeschke, John H. Juhl, John R. Pellett, William Stead

New Jersey

Dr. Julian Johnson, Philadelphia, will deliver the Seventh Selman Waksman Lecture of the New Jersey Chapter at its meeting at Haddon Hall, Atlantic City on May 17. Dr. Johnson will speak on The Present Status of Cardiac Surgery.

New Mexico Chapter

The New Mexico Chapter will meet for dinner on May 19 in Santa Fe. On May 20, the Chapter will present a Symposium on Tuberculosis to include the medical and socio-economic aspects.

Kansas Chapter

The annual meeting of the Kansas Chapter will take place at the Broadview Hotel, Wichita, May 3, in conjunction with the meeting of the state medical society. Dr. Benjamin Matassarin, Wichita, chapter president, will preside over the program as follows:

1:30 p.m. Surgical Lesions of the Esophagus
Robert G. Rate, Halstead

Carcinoma of the Lung
Robert M. Brooker, Topeka

Anomalous Lung (film)
Calvin R. Openshaw, Hutchinson

Pulmonary Artery Banding, Its Application in Congenital Heart Disease
C. Frederick Kittle, Kansas City

Pitfalls of Cardiac Surgery
Ben H. Buck, Wichita

Left Sided Cardiac Diagnostic Techniques
R. L. Sifford, Wichita

Panel discussion: Chemotherapy of Inoperable Pulmonary Malignancy
John K. Fulton, Wichita; William E. Larsen, Kansas City; John G. Shellito, Wichita

Congenital Lobar Emphysema in Infants
Paul J. Uhlig, Wichita

X-ray Conference

5:00 p.m. Social hour

Puerto Rico Chapter

New officers of the Puerto Rico Chapter of the College are:

President	Juan Ramon Marchand, Santurce (re-elected)
Vice President	Hilarion Sanchez, Rio Piedras (re-elected)
Secretary-Treasurer	Vidal Francis Lizardo, Bayamon

MEDICAL SERVICE BUREAU

POSITIONS WANTED

Anesthesiologist, subspecialty chest disease, exceptionally qualified for academic or clinical position, seeks directorship of department or similar senior situation. Curriculum vitae available. Please address inquiries to Box 313B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Experienced medical photographer desires permanent position. Excellent references, international awards and extensive experience in cardiac, pulmonary and neurologic surgery. Fifteen years motion picture producing, directing, cameraman, editing and sound recording. Married. Requires top salary. Please address inquiries to Box 314B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Physician, 43, certified internal medicine-cardiovascular disease, university trained, FACP, FACA, FACC, dissatisfied with successful private practice; desires association with group, hospital or medical school allowing teaching and research. Prefers southwest; licensed in California. Please address inquiries to Box 315B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Physician wanted to work in division of pulmonary diseases. Must be licensed by a state or have immigrant visa and be certified by ECFMG. Active medical and surgical program for all types of diseases of the chest. Large out-patient clinic. Training in cardiopulmonary laboratory provided, including cardiac catheterization. Good salary. Available immediately. Apply to: Dr. Rufus Little, Superintendent, Bergen Pines County Hospital, Paramus, New Jersey.

Full-time physician wanted for new 300-bed tuberculosis division of Baltimore City Hospitals. Associated with two medical schools for teaching purposes with opportunity for research. Complete surgical and pathological facilities. Starting salary $8640 with annual increases to $11,000. Permanent employment under municipal Civil Service Commission. Please address inquiries to Director of Personnel, Baltimore City Hospitals, Baltimore 24, Maryland.

Physician wanted for moderate-sizeo chest disease hospital. Residency training pulmonary and heart diseases; man, 28-40 years, preferably single, graduate approved school. Exchange visitors are not eligible. Opportunity for advancement. Must have ECFMG or New York state license if not U. S. citizen. Please write: Will Rogers Memorial Hospital, Saranac Lake, New York.